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(54) Title: A NOVEL POLYMORPH OF SERTRALINE HYDROCHLORIDE AND COMPOSITION CONTAINING THEREOF, NOVEL METHODS FOR PREPARATION OF SERTRALINE HYDROCHLORIDE POLYMORPHS AND AMORPHOUS FORM

(57) Abstract: Novel methods for the preparation of sertraline hydrochloride Forms II, III, V, VI, VII, VIII, IX and X. Novel Form II is also disclosed. According to the present invention, sertraline hydrochloride Form II may be produced directly form sertraline base or sertraline mandelate. It may also be produced from sertraline hydrochloride solvate and hydrate forms, and crystallized form new solvent systems. According to the present invention, sertraline hydrochloride form III may be produced by heating sertraline hydrochloride Forms V and VI. Sertraline hydrochloride Forms V and VI may be produced from either sertraline hydrochloride or sertraline base by crystallization. Sertraline hydrochloride Form VII may be produced by suspending sertraline chloride polymorph V in water, followed by filtration. Sertraline hydrochloride Forms VIII and IX may be produced by suspending sertraline base in water followed by acidification and filtration. Sertraline hydrochloride Form X may be produced by suspending sertraline hydrochloride in benzyl alcohol with heating, followed by filtration. Pharmaceutical compositions containing sertraline hydrochloride Forms II, III and V through X, and methods of treatment using such pharmaceutical compositions are also disclosed.

A NOVEL POLYMORPH OF SERTRALINE HYDROCHLORIDE AND COMPOSITIONS CONTAINING THEREOF, NOVEL METHODS FOR PREPARATION OF SERTRALINE HYDROCHLORIDE POLYMORPHS AND AMORPHOUS FORM

CROSS-REFERENCE TO RELATED APPLICATIONS

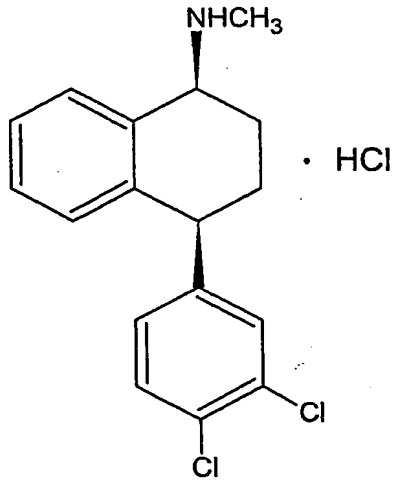
This application corresponds to U.S. patent application Serial No. 09/575,634, filed May 22, 2000, and Serial No. 09/586,842, filed June 5, 2000. U.S. Serial No. 09/575,634, filed May 22, 2000 claims priority to U.S. provisional application Serial No. 60/182,159, filed February 14, 2000. U.S. application Serial No. 09/586,842, filed June 5, 2000 is a continuation-in-part of U.S. application Serial No. 09/448,985, filed November 24, 1999, which claims the benefit of U.S. provisional application No. 60/147,888, filed August 9, 1999. The contents of each of these applications are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to novel crystalline Form II its pharmaceutical compositions, and reproducible methods for the preparation of sertraline hydrochloride crystalline Forms II, III and V through X, as well as the preparation of amorphous form of sertraline hydrochloride.

BACKGROUND OF THE INVENTION

Sertraline hydrochloride, (1S-cis)-4-(3,4 dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride, having the formula



is approved, under the trademark Zoloft®, by the U.S. Food and Drug Administration, for the treatment of depression, obsessive-compulsive disorder and panic disorder.

U.S. Patent No. 4,536,518 ("the '518 patent") describes the preparation of sertraline hydrochloride with a melting point of 243-245°C by treating an ethyl acetate/ether solution of the free base with gaseous hydrogen chloride. The solid state properties of the sertraline hydrochloride so produced are not otherwise disclosed.

According to U.S. Patent No. 5,248,699 ("the '699 patent"), the sertraline hydrochloride produced by the method of the '518 patent has a crystalline form denominated "Form II." The '699 patent discloses four other polymorphs I, III, IV, and V, and characterizes them by single crystal x-ray analysis, powder x-ray diffraction, infra-red spectroscopy, and differential scanning calorimetry. The '699 patent reports that Form II is produced by rapid crystallization of sertraline hydrochloride from an organic solvent, including isopropyl alcohol, ethyl acetate or hexane, and generally describes methods for making sertraline hydrochloride Forms I-V. According to this patent, the preferential formation of Forms I, II or IV in an acidic solution consisting of isopropyl alcohol, hexane, acetone, methyl isobutyl ketone, glacial acetic acid or, preferably, ethyl acetate, depends on the rapidity of crystallization. Form I is described as being made by crystallizing sertraline hydrochloride in an acidic solution using an organic solvent such as those listed above. The crystallization of Form I is carried out at a temperature from about 20°C to about the solvent reflux temperature, preferably from about 40° to 60°C. The only method described in this patent for making Forms II and IV is by the rapid crystallization of sertraline hydrochloride from an organic solvent such as those listed above. Slow crystallization or granulation of sertraline hydrochloride is said to produce Form I. Form III is described as being formed by heating Forms I, II or IV to temperatures above about 180° C. Granulating either of Forms II, III or IV in any of the solvents listed above at a temperature from about 40°C to 60°C is said to cause conversion to Form I. The only method described in this patent for making Form V is by sublimation of sertraline hydrochloride Form I at reduced pressure and at a temperature from about 180-190°C. However, in our hands attempts to repeat this procedure to obtain Form V have been unsuccessful.

The experimental procedure for the preparation of sertraline hydrochloride described

in the '518 patent, was repeated in the laboratory. According to the '699 patent, the '518 procedure produces sertraline hydrochloride Form II. Four experiments were performed according to the description in the '518 patent. By following the procedures described in the '699 patent for preparation of sertraline hydrochloride Form II, we were unable to obtain sertraline hydrochloride Form II. Thus there remains a need for reproducible methods for the preparation of sertraline hydrochloride Form II.

SUMMARY OF THE INVENTION

The present invention relates to a process for making sertraline hydrochloride Form II comprising the steps of dissolving sertraline base or sertraline mandelate in an organic solvent to form a solution; adding hydrogen chloride to the solution; heating the solution to a temperature between about room temperature and about reflux for a time sufficient to induce the formation of sertraline hydrochloride Form II; and isolating sertraline hydrochloride Form II.

The present invention also relates to a process for making sertraline hydrochloride Form II comprising the steps of dissolving sertraline hydrochloride in dimethylformamide, cyclohexanol, acetone or a mixture thereof; heating the solution for a time sufficient to affect transformation to sertraline hydrochloride Form II; and isolating sertraline hydrochloride Form II.

The present invention further relates to a process for making sertraline hydrochloride Form II comprising the steps of granulating sertraline hydrochloride Form V in ethanol or methanol; and stirring the mixture of sertraline hydrochloride Form V and ethanol or methanol for a time sufficient to induce transformation to sertraline hydrochloride Form II.

The present invention still further relates to a process for making a mixture of sertraline hydrochloride Form II and Form V comprising the steps of heating sertraline hydrochloride ethanolate Form VI at up to 1 atmosphere pressure; and isolating a mixture of sertraline hydrochloride Form II and Form V.

The present invention still further relates to a process for making sertraline hydrochloride Form II comprising the steps of suspending a water or solvent adduct of sertraline hydrochloride in a solvent selected from the group consisting of acetone, t-butyl-methyl ether, cyclohexane, n-butanol, and ethyl acetate such that a slurry is formed, for a

time sufficient to effect transformation to sertraline hydrochloride Form II; and filtering the slurry to isolate sertraline hydrochloride Form II.

The present invention still further relates to sertraline hydrochloride Form II, characterized by an x-ray powder diffraction pattern comprising peaks at about 5.5, 11.0, 12.5, 13.2, 14.7, 16.4, 17.3, 18.1, 19.1, 20.5, 21.9, 22.8, 23.8, 24.5, 25.9, 27.5, and 28.0 degrees two theta; pharmaceutical compositions for the treatment of depression comprising sertraline hydrochloride Form II together with a pharmaceutically acceptable carrier, and a method for treating depression comprising the step of administering to a subject in need of such treatment a therapeutically effective amount of the such a pharmaceutical composition.

The present invention also relates to a process for making sertraline hydrochloride Form V comprising the steps of: dissolving or suspending sertraline hydrochloride in a suitable solvent; removing the solvent; and drying to form sertraline hydrochloride Form V.

The present invention also relates to a process for making sertraline hydrochloride Form V comprising the steps of: dissolving or suspending sertraline base in a solvent; adding hydrogen chloride to the solvent to reduce the pH of the solution or suspension; and isolating sertraline hydrochloride Form V from the solution or suspension.

The present invention also relates to a process for making sertraline hydrochloride Form V comprising the step of drying sertraline hydrochloride Form VII.

The present invention also relates to a process for making sertraline hydrochloride Form V comprising the steps of: dissolving or suspending sertraline hydrochloride in water; adding a sufficient amount of hydrochloric acid or hydrogen chloride to facilitate precipitation of sertraline hydrochloride; removing the water; and isolating sertraline hydrochloride Form V.

The present invention also relates to a process for making sertraline hydrochloride Form VI comprising the steps of: dissolving sertraline base in a solvent; adding hydrochloric acid to the solvent; and isolating sertraline hydrochloride Form VI without further drying.

The present invention also relates to a process for making sertraline hydrochloride Form VI comprising the steps of: dissolving or suspending sertraline hydrochloride in

ethanol or methanol; stirring for a time sufficient to induce the transformation of sertraline hydrochloride to sertraline hydrochloride Form VI; and isolating sertraline hydrochloride Form VI.

The present invention also relates to a process for making sertraline hydrochloride Form VIII comprising the steps of: suspending sertraline base in water; adding hydrogen chloride to the water; and filtrating the precipitate so obtained without further drying.

The present invention also relates to a process for making sertraline hydrochloride Form VIII comprising the steps of: suspending or dissolving sertraline hydrochloride ethanolate Form VI or sertraline hydrochloride Form II in water or a mixture of water and isopropyl alcohol; and isolating sertraline hydrochloride Form VIII.

The present invention also relates to a process for making sertraline hydrochloride Form III comprising the steps of: heating sertraline hydrochloride Form V or Form VI to a temperature sufficient, and for a time sufficient, to induce the transformation of sertraline hydrochloride Form V or Form VI to sertraline hydrochloride Form III; and isolating sertraline hydrochloride Form III.

The present invention also relates to a process for making amorphous sertraline hydrochloride comprising the steps of: suspending or dissolving sertraline base in a non-polar organic solvent; adding gaseous hydrochloric acid; and isolating amorphous sertraline hydrochloride.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride prepared by the methods of U.S. Patent No. 4,536,518.

Figure 2 is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride prepared by the methods of U.S. Patent No. 5,248,699.

Figure 3 is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form II prepared by the methods of the present invention.

Figure 4 is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form V.

Figure 5 is a characteristic x-ray powder diffraction spectrum of amorphous sertraline hydrochloride.

Figure 6 is a characteristic differential scanning calorimetric (DSC) thermogram of sertraline hydrochloride Form V.

Figure 7 is a characteristic infrared (IR) absorption spectrum of sertraline hydrochloride Form V.

Figure 8 is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form VI.

Figure 9 is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form VII.

Figure 10 is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form VIII.

Figure 11 is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form IX.

Figure 12 is a characteristic differential scanning calorimetric (DSC) thermogram of sertraline hydrochloride Form VIII.

Figure 13 is a characteristic differential scanning calorimetric (DSC) thermogram of sertraline hydrochloride Form IX.

Figure 14 is a characteristic infrared (IR) absorption spectrum of sertraline hydrochloride Form VIII.

Figure 15 is a characteristic infrared (IR) absorption spectrum of sertraline hydrochloride Form IX.

Figure 16 is a characteristic differential scanning calorimetric (DSC) thermogram of sertraline hydrochloride Form VI.

Figure 17 is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form X.

Figure 18 is a characteristic infrared (IR) absorption spectrum of sertraline hydrochloride Form X.

Figure 19 is a characteristic differential scanning calorimetric (DSC) thermogram of sertraline hydrochloride Form X.

DETAILED DESCRIPTION OF THE INVENTION

Form II

The present invention provides new processes for making sertraline hydrochloride Form II from sertraline base or sertraline mandelate. Sertraline base may be made by methods known in the art, including the methods of the '518 patent. Sertraline base is dissolved in a suitable solvent. Suitable solvents include ethyl acetate, acetone, t-methyl-butyl ether, isopropyl alcohol, n-butanol, t-butanol, iso-butanol, hexane, and cyclohexane, and mixtures thereof. The pH of the sertraline base solution is lowered by the addition of hydrogen chloride, which may result in a temperature increase. As used herein, "hydrogen chloride" includes both gaseous hydrogen chloride and aqueous hydrogen chloride (*i.e.* hydrochloric acid). Hydrogen chloride also may be added as a solution with an organic solvent, such as a solution of isopropyl alcohol and hydrogen chloride, n-butanol and hydrogen chloride, acetone and hydrogen chloride, or the like. The solution of sertraline base or sertraline mandelate in the solvent is heated to a temperature between about room temperature and the reflux temperature of the solvent and maintained at that temperature for a period of time sufficient to effect the transformation to sertraline hydrochloride Form II. Preferably the solution is heated to a temperature between about 45°C and the reflux temperature of the solvent. Most preferably the solution is heated to at or about the reflux temperature of the solvent. Upon cooling of the mixture, for example to room temperature, sertraline hydrochloride Form II is isolated by filtration.

In a preferred variation of this method, the solution of sertraline base or sertraline mandelate in a solvent is heated to the reflux temperature of the solvent. The mixture is refluxed for a time sufficient to effect the transformation to sertraline hydrochloride Form II. Preferably the mixture is refluxed for about 1 to 4 hours.

Numerous experiments were performed in an attempt to repeat the procedure described in U.S. Patent No. 4,536,518 for preparing Form II wherein sertraline base was dissolved in ethyl acetate, ether was added and the solution was acidified with gaseous hydrogen chloride. The material obtained after filtration and air drying was sertraline hydrochloride amorphous, not Form II as was expected. These experiments are set forth in Examples 13-16 below.

The x-ray powder diffraction graphs for the products of each of these experiments are

equivalent, containing peaks at 11.0, 12.0, 15.4, 16.2, 22.4, 22.9 degree two-theta (See Figure 1 for a representative example). Figure 1 does not contain the typical peaks of sertraline hydrochloride Form II, indicating an absence of sertraline hydrochloride Form II in those samples. Thus, none of these experiments, which follow the procedure described in the '518 patent for preparation of sertraline hydrochloride Form II, leads to sertraline hydrochloride Form II.

The '699 patent provides experimental procedures for preparation of sertraline hydrochloride. The '699 patent does not provide experimental procedure for preparation of sertraline hydrochloride Form II, but it is mentioned that sertraline hydrochloride Form II may be prepared by "rapid crystallization" from the same solvents.

The procedure of the '699 patent was repeated in an attempt to prepare sertraline hydrochloride form II from ethyl acetate. In a trial of the methods according to the '699 patent: An aqueous solution of sodium hydroxide, 10 %, was added to a slurry of sertraline mandelate crystals (44.6 g) in ethyl acetate (290 mL), until complete dissolution. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (280 mL) and combined with the organic phase. The resulting organic solution was washed with water (5 x 100 mL) then with brine (100 mL) and concentrated on a rotavapor to a volume of 356 mL. The concentrated solution was cooled to 58°C and seeded with sertraline hydrochloride Form II. Concentrated hydrochloric acid (32 %, 8.1 mL) was added to this solution. The solution was then rapidly cooled to 30°C over 5 minutes. A heavy gel was obtained and the stirring was continued overnight. The solid was filtrated, washed with ethyl acetate and dried at 50°C. The dried solid, sertraline hydrochloride, was not sertraline hydrochloride Form II, as shown by the x-ray diffraction pattern of Figure 2.

By following the procedures described in the '699 patent for preparation of sertraline hydrochloride Form II, we did not obtain sertraline hydrochloride Form II. It is thus apparent that neither the '699 patent nor the '518 patent disclose a useful method for the preparation of sertraline hydrochloride Form II.

The present invention also provides new processes for making sertraline hydrochloride Form II from sertraline hydrochloride Form V by granulation. In the conversion of sertraline hydrochloride Form V to sertraline hydrochloride Form II, sertraline hydrochloride Form V is combined with a small amount of ethanol or methanol.

The mixture of sertraline hydrochloride Form V and ethanol or methanol is stirred for at least a period of at least a few hours, up to several days, preferably about two days, to induce the transformation of Form V to Form II. Sertraline hydrochloride Form II is then isolated by filtration.

The present invention also provides new processes for making sertraline hydrochloride Form II by recrystallization of sertraline hydrochloride under heating conditions. In the conversion of sertraline hydrochloride to sertraline hydrochloride Form II, sertraline hydrochloride is dissolved in a suitable organic solvent. The solution is then heated for a time sufficient to effect transformation to sertraline hydrochloride Form II. Suitable solvents include dimethylformamide, cyclohexanol and acetone. Dimethylformamide is preferred. The suspension may be heated to a temperature between about 70°C and 120°C. Sertraline hydrochloride Form II is then isolated by filtration.

The present invention provides new processes for making sertraline hydrochloride Form II from sertraline hydrochloride Form VI, Form VII or Form VIII by reslurry in organic solvents at temperatures between 25-80°C, followed by drying. Sertraline hydrochloride Form VI may be made following the methods of Examples 2 and 3. Sertraline hydrochloride Form VII is a water adduct and may be made by the methods of Examples 19 and 20. Sertraline hydrochloride Form VIII may be made by the methods of Examples 17 and 18. The methods provided in the present invention have advantages over the rapid recrystallization method of U.S. Patent No. 5,248,699. The method of the present invention does not require complete dissolution of sertraline hydrochloride, controlling the rate of heating or cooling of a sertraline solution, or controlling the rate of crystallization. The present method utilizes less solvent than the method of the '699 patent, since the sertraline hydrochloride starting material need not be completely dissolved.

In the conversion of sertraline hydrochloride Form VI, Form VII or Form VIII to sertraline hydrochloride Form II, according to the present invention, sertraline hydrochloride Form VI, Form VII water adduct, or Form VIII is combined with an aprotic organic solvent to form a slurry. Suitable solvents include n-butanol, acetone, t-butyl-methyl ether (MTBE), ethyl acetate and cyclohexane. The conversion may take place at room temperature, but preferably the sertraline hydrochloride Form VI, Form VII water

adduct, or VIII and solvent are heated to temperatures between 25°C and 80°C. About 1 to about 10 volumes of solvent are preferred, based on the weight of the sertraline hydrochloride starting material. See Examples 8 (3 volumes of solvent) and 9 (5 volumes of solvent) below. Smaller amounts of solvent will also effect the transformation, albeit in some instances more slowly. The reaction is carried out for a time sufficient to convert the Form VI, Form VII or Form VIII to Form II. We have not observed any further conversion of Form II upon treatment under these conditions for times longer than the minimum time necessary to effect the transformation.

The present invention also provides new processes for making a mixture of sertraline hydrochloride Form II and sertraline hydrochloride Form V. In this embodiment of the present invention, sertraline hydrochloride Form VI is heated to induce the transformation of sertraline hydrochloride Form VI to a mixture of both sertraline hydrochloride Form II and sertraline hydrochloride Form V. In this embodiment of the present invention, the heating of sertraline hydrochloride Form VI may be done under reduced pressure or atmospheric pressure.

Form V

The present invention provides new processes for making sertraline hydrochloride Form V from sertraline hydrochloride, sertraline base or amorphous sertraline hydrochloride. The methods provided in the present invention are more commercially practicable than the sublimation-condensation method of U.S. Patent No. 5,248,699, which we have not been able to reproduce. It has also surprisingly been found that, by the present method, Form V is formed even at different crystallization rates.

Where the present invention provides methods for the conversion of sertraline hydrochloride to sertraline hydrochloride Form V, in one embodiment sertraline hydrochloride is combined with a solvent. Suitable solvents include methanol, ethanol, 1-methoxy-2-propanol, trichloroethane, water, and mixtures thereof. If a mixture of isopropyl alcohol and water is used, it is preferably an about 6:1 mixture. Preferably the solvent is methanol, ethanol, or mixtures thereof, and most preferably the solvent is ethanol. Sertraline hydrochloride Form V is then isolated by allowing the solution to cool. One preferred method is to rapidly cool the solvent to 5°C. Another preferred method comprises seeding the solution with sertraline hydrochloride Form V crystals, followed by

slow cooling to room temperature, followed by filtration and drying.

Alternatively, Form V may be obtained by forming a solution or suspension of sertraline hydrochloride in a suitable solvent and spray drying the solution or suspension. Preferred solvents include water and water/alcohol mixtures.

The present invention also provides methods for the conversion of sertraline hydrochloride to sertraline hydrochloride Form V wherein the solvate sertraline hydrochloride Form VI (described in more detail below) is an intermediate. In this embodiment of the present invention, sertraline hydrochloride is suspended or dissolved in either methanol or ethanol or mixtures thereof thereby forming sertraline hydrochloride Form VI. This intermediate sertraline hydrochloride Form VI is then dried, with or without a separate isolation step, to remove all solvent and sertraline hydrochloride Form V is isolated. Sertraline hydrochloride Form V can also be prepared by suspending or dissolving sertraline hydrochloride solvate Form VI in water.

Sertraline hydrochloride Form V can also be prepared by drying Form VII (described in more detail below). In this embodiment of the present invention, sertraline hydrochloride Form V is dried at 80°C overnight thereby forming sertraline hydrochloride Form V.

The present invention also provides methods for the conversion of sertraline hydrochloride to sertraline hydrochloride Form V wherein the sertraline hydrochloride Form VIII (described in more detail below) is an intermediate. In this embodiment of the present invention, sertraline hydrochloride Form II is suspended or dissolved in water thereby forming sertraline hydrochloride Form VIII. This intermediate sertraline hydrochloride Form VIII is then dried, with or without a separate isolation step, to remove all solvent and sertraline hydrochloride Form V is isolated. Methods for the preparation of sertraline hydrochloride Form II are disclosed in U.S. applications serial nos. 09/448,985 filed November 24, 1999 and 09/575,634 filed May 22, 2000, the contents of which are hereby incorporated by reference.

The present invention also provides methods for the conversion of sertraline base to sertraline hydrochloride Form V. In one such embodiment, sertraline base is added to at least one solvent, and hydrogen chloride gas is bubbled through the solution. Suitable solvents include methanol, ethanol, water, ethyl acetate, isopropyl alcohol, ether, hexane,

and toluene, and mixtures thereof. Alternatively, an appropriate amount of hydrogen chloride gas dissolved in a suitable solvent and then combined with the sertraline base solution. As used herein, "hydrogen chloride" includes both gaseous hydrogen chloride and aqueous hydrogen chloride (*i.e.* hydrochloric acid). Sertraline hydrochloride Form V is isolated by allowing precipitation to occur from about 0°C to about 60°C followed by filtration and drying. Preferred solvents include methanol, ethanol, hexane, isopropyl alcohol, or mixtures thereof. In a variation of this method, sertraline base is added to a suitable solvent and the resulting solution is added to a hydrochloric acid solution of pH 0-4; preferably the pH of the solution is about 1.

Alternatively, sertraline base is added to a solvent. The solution is heated and concentrated hydrochloric acid is added. Water may also be added. The solvent may be partially removed by distillation. Sertraline hydrochloride Form V is isolated by allowing the mixture to cool to room temperature and remain at room temperature overnight, followed by filtration and drying. Suitable solvents for use in this method include methanol, ethanol, water, hexane, isopropyl alcohol, and ethyl acetate, and mixtures thereof.

Alternatively, sertraline base may be combined with a solvent selected from the group consisting of methanol, ethanol and a mixture thereof. A saturated solution of hydrogen chloride gas in isopropyl alcohol is added to induce formation of sertraline hydrochloride Form V. Sertraline hydrochloride Form V is isolated by allowing the solution to stand at room temperature overnight, followed by filtration and drying of the precipitate.

Form V may also be obtained by forming a suspension of sertraline base and hydrochloric acid in water or a water/ethanol mixture and spray drying the suspension. In this embodiment of the present invention, the solution or suspension of sertraline base and hydrochloric acid is sprayed into a heated chamber. The temperature of the chamber is such that the solvent is removed thus forming sertraline hydrochloride Form V.

Sertraline base for use in the processes of the present invention may be produced by dissolving sertraline mandelate in ethyl acetate followed by neutralization of the sertraline mandelate with aqueous sodium hydroxide. The organic phase is separated from the aqueous phase and dried using magnesium sulfate. The solvent is removed under reduced pressure to produce sertraline base as an oil. Methods for making sertraline base are set

forth in U.S. Patent Nos. 4,536,518 and 5,248,699, the contents of which are incorporated herein by reference.

Where the present invention provides methods for the conversion of amorphous sertraline hydrochloride to sertraline hydrochloride Form V, amorphous sertraline hydrochloride is kept in a closed container, such as a bag, and warmed to about 40°C to about 80°C or is stored at room temperature for a period between a few hours and several days depending on the temperature.

The sertraline hydrochloride Form V that results from practicing the invention as exemplified herein can be characterized by its powder X-ray diffraction pattern. Figure 4 is a representative pattern of sertraline hydrochloride Form V. The principal peaks observed are at about 5.2° ±0.2, 10.4° ±0.2, 11.0° ±0.2, 14.3° ±0.2, 16.5° ±0.2, 17.3° ±0.2, 18.4° ±0.2, 19.1°±0.2, 19.7° ±0.2, 20.9° ±0.2, 22.0° ±0.2, 23.2° ±0.2, 23.6° ±0.2, 25.5° ±0.2, 26.0 °±0.2, and 29.1° ±0.2 degrees 2 theta.

Three experiments were performed in order to repeat the procedure described in U.S. Patent No. 5,248,699 for preparing Form V by sublimation. Two experiments were performed by sublimating a sample of Form I under 30 mm Hg vacuum and temperature between 170-190°C. A third experiment was performed by sublimating a sample of Form I under high vacuum (0.1 mm Hg) and temperature between 180-195°C.

The three samples of sertraline hydrochloride prepared by sublimation were analyzed by powder x-ray diffraction. In all cases, the typical broad featureless pattern without sharp peaks typical of amorphous materials was obtained. Figure 5 is one such pattern.

In conclusion, sertraline hydrochloride could not be obtained by following the procedure set forth in U.S. Patent No. 5,248,699 for preparing Form V by sublimation of Form I.

The IR spectrum of sertraline hydrochloride Form V produced by the present process is characterized by the following bands: 773 cm^{-1}, 822 cm^{-1}, 1012 cm^{-1}, 1032 cm^{-1}, 1054 cm^{-1}, 1133 cm^{-1}, 1328 cm^{-1}, 1562 cm^{-1}, and 1590 cm^{-1}, as shown in Figure 7.

The sertraline hydrochloride Form V of the present process is further characterized by the DSC thermogram data, for example, as disclosed in Figure 6. The DSC thermogram is characterized by a small endotherm (~3 Joule per gram) at about 210°C, believed to be a solid-solid transformation (based upon observation under a hot stage microscope) to Form

III, and a melting peak 251°C.

Form VI

Sertraline hydrochloride Form VI is a solvated crystal form of sertraline hydrochloride. Sertraline hydrochloride Form VI may be an ethanolate, wherein ethanol is incorporated into the crystal structure of Form VI. Alternatively, sertraline hydrochloride Form VI may be a methanolate, wherein methanol is incorporated into the crystal structure of sertraline hydrochloride Form VI. All sertraline hydrochloride Form VI solvates have identical powder x-ray diffraction patterns. Therefore, when referring to sertraline hydrochloride Form VI all sertraline hydrochloride Form VI solvates, such as sertraline hydrochloride Form VI ethanolate and sertraline hydrochloride Form VI methanolate, are necessarily included.

To form the novel crystalline form sertraline hydrochloride Form VI, sertraline base is added to the appropriate solvent. Which solvent is appropriate will depend on which solvate is to be formed, e.g. ethanol (to form the ethanolate) and methanol (to form the methanolate). Hydrogen chloride gas is then bubbled through the solution. Sertraline hydrochloride Form VI is isolated by allowing precipitation to occur, followed by filtration. The DSC thermogram of Form VI crystallized from ethanol displays a desolvation peak at 95°C (see Fig. 16) and loses 11.2% weight (by TGA); Form VI crystallized from methanol loses 8.3 % weight (by TGA) upon desolvation. Form VI crystallized from ethanol is an ethanolate, and more specifically is a monoethanolate. Form VI crystallized from methanol is a methanolate, and more specifically is a monomethanolate.

The present invention also provides new processes for making sertraline hydrochloride solvate Form VI by reslurry of other sertraline hydrochloride crystalline forms. In the conversion of sertraline hydrochloride to sertraline hydrochloride ethanolate Form VI, sertraline hydrochloride is dissolved in the appropriate solvent and stirred for about 18-36 hours; 24 hours is preferred. Sertraline hydrochloride solvate Form VI is isolated by a suitable method, such as filtration. Sertraline hydrochloride Forms I, II, III, IV, V and X are suitable for use as starting materials in this process.

The sertraline hydrochloride Form VI so isolated is a solvate and exhibits the powder x-ray diffraction pattern of Figure 8, comprising peaks at 7.3°±0.2, 12.1°±0.2, 12.7°±0.2,

14.0°±0.2, 15.6°±0.2, 17.6°±0.2, 20.1°±0.2, 20.6°±0.2, 21.9°±0.2, 22.7°±0.2, 23.0°±0.2, 23.8°±0.2, 24.3°±0.2, 25.4°±0.2, and 26.3°±0.2 degrees two-theta. Drying of the precipitated sertraline hydrochloride Form VI at 50-60°C overnight yields sertraline hydrochloride Form V.

Form VII

It has also been discovered that a new crystalline form of sertraline hydrochloride, designated Form VII, may be obtained by suspending or dissolving Form V in water, and filtrating the suspension after one day without further drying.

In another embodiment of the invention, sertraline hydrochloride Form VII is made from sertraline hydrochloride Form VI. Sertraline hydrochloride Form VI is dispersed in water and the mixture is heated to facilitate the dissolution of sertraline hydrochloride Form VI. The solution may be heated to between about 30°C and about 90°C, preferably to about 80°C. The pH is then lowered, preferably to about pH 1, and the mixture is allowed to cool to room temperature and stirred until the reaction is complete. Preferably the reaction is stirred for two hours at room temperature. Sertraline hydrochloride Form VII is isolated by filtration and washing with water.

As shown in Figure 9, sertraline hydrochloride Form VII is characterized by two unique strong x-ray powder diffraction peaks at 4.0°±0.2, and 20.0 degrees two-theta and medium intensity peaks at 8.0° ±0.2, 11.6°±0.2, 12.0 ±0.2, 13.8°±0.2, 16.5°±0.2, 22.8°±0.2, 24.1°±0.2, 25.0°±0.2, 26.6°±0.2, 30.7°±0.2, 34.7°±0.2 2 two-theta. The TGA curve shows a loss on drying of about 45%.

Forms VIII and IX

Additional new crystalline forms of sertraline hydrochloride, Forms VIII and IX, have also been discovered. Sertraline hydrochloride hydrate Form VIII may be produced by suspending sertraline base in water and heating, followed by acidification and filtration. Form IX is obtained by drying of Form VIII. Preferably the sertraline base is suspended in water, the suspension heated to a temperature between about 30°C and about 80°C. Hydrogen chloride is added to reduce the pH, preferably to between about 1 to about 4, and the resulting solution is cooled to room temperature.

The present invention also provides new processes for making sertraline hydrochloride Form VIII from sertraline hydrochloride ethanolate Form VI. In one

embodiment of the present invention, a slurry of sertraline hydrochloride ethanolate Form VI in water or a mixture of water and isopropyl alcohol is stirred, preferably for about one hour. The slurry is then filtered and washed with water and sertraline hydrochloride hydrate Form VIII is isolated.

The present invention also provides precesses of making sertraline hydrochloride Form VIII from sertraline hydrochloride Form II. In the conversion of sertraline hydrochloride Form II to sertraline hydrochloride Form VIII, sertraline hydrochloride Form II is suspended in water or a mixture of water and isopropyl alcohol and stirred, preferably overnight, and sertraline hydrochloride hydrate Form VIII is isolated by filtration.

Sertraline hydrochloride Form VIII is characterized by x-ray powder diffraction peaks at 4.7°±0.2, 11.8° ±0.2, 16.3°±0.2, 17.8°±0.2, 19.6°±0.2, 23.2°±0.2, 24.2°±0.2, 25.1°±0.2, and 26.0°±0.2 two-theta, as described in Figure 10.

The DSC thermogram for Form VIII is characterized by a strong endotherm below 100°C, small endothermic and exothermic events at about 220°C and a melting peak at 247°C as described in Figure 12.

The TGA curve shows a loss on drying step of about 20% below 100°C.

The IR spectrum of Form VIII is characterized by the following bands: 740 cm^{-1}, 779 cm^{-1}, 822 cm^{-1}, 887 cm^{-1}, 915 cm^{-1}, 1031 cm^{-1}, 1053 cm^{-1}, 1110 cm^{-1}, 1134 cm^{-1}, 1153 cm^{-1}, 1217 cm^{-1}, 1307 cm^{-1}, and 1377 cm^{-1}, as described in Figure 14.

Sertraline hydrochloride Form IX is characterized by x-ray powder diffraction peaks at 5.1°±0.2, 14.2°±0.2, 15.8°±0.2, 16.8°±0.2, 19.2°±0.2, 19.7°±0.2, 22.4°±0.2, 23.2°±0.2, 25.3°±0.2 and 26.1°±0.2 two-theta, as described in Figure 11.

The IR spectrum of Form IX is characterized by the following bands: 701 cm^{-1}, 715 cm^{-1}, 741 cm^{-1}, 758 cm^{-1}, 780 cm^{-1}, 816 cm^{-1}, 823 cm^{-1}, 1030 cm^{-1}, 1053 cm^{-1}, 1078 cm^{-1}, 1110 cm^{-1}, 1204 cm^{-1}, 1217 cm^{-1}, 1307 cm^{-1}, and 1350 cm^{-1}, as described in Figure 15.

Form X

It has further been discovered that another crystalline form of sertraline hydrochloride, denominated Form X, may be obtained by suspending sertraline hydrochloride in benzyl alcohol, and heating to facilitate dissolution. The solution is cooled and the precipitate filtered, washed with benzyl alcohol and dried, to yield sertraline hydrochloride Form X.

The Form X produced in this manner is characterized by a powder x-ray diffraction

pattern having its principal peaks at 15.0°±0.2, 16.0°±0.2, 16.5°±0.2, 17.0°±0.2, 18.1°±0.2, 21.0°±0.2, 22.4°±0.2, 24.9°±0.2, 25.4°±0.2, 26.2°±0.2, 27.1°±0.2, 28.4°±0.2, and 29.0°±0.2 degrees two-theta as described in Figure 17.

The IR spectrum of Form X is characterized by the following bands: 742 cm^{-1}, 776 cm^{-1}, 806 cm^{-1}, 824 cm^{-1}, 1002 cm^{-1}, 1017 cm^{-1}, 1028 cm^{-1}, 1060 cm^{-1}, 1079 cm^{-1}, 1135 cm^{-1}, 1218 cm^{-1}, 1314 cm^{-1}, 1336 cm^{-1}, and 1560 cm^{-1} as described in Figure 18.

The DSC of Form X shows a small endotherm at about 190°C followed by a melting endotherm at about 250°C (see Figure 19).

Form III

The present invention provides new processes for making sertraline hydrochloride Form III from sertraline hydrochloride Forms V and VI. In the conversion of sertraline hydrochloride Form V to sertraline hydrochloride Form III, Form V is heated to a temperature between about 150°C and about 180°C for about 3 hours to about 2 days to induce the formation of sertraline hydrochloride Form III. Heating for 24 hours is preferred. The reaction may be stirred. The method of the present invention has the advantage of using no solvent.

Amorphous Sertraline Hydrochloride

In an embodiment of the present invention, amorphous sertraline is made by dissolving sertraline hydrochloride in water or a water/alcohol mixture and drying the solution by the spray dryer technique. Amorphous sertraline hydrochloride may also be made by sublimation of sertraline hydrochloride.

The amorphous sertraline hydrochloride produced by methods of the present invention is characterized by a powder x-ray diffraction pattern having the typical broad featureless pattern without sharp peaks typical of amorphous materials. Figure 5 is one such pattern.

Experimental

The powder X-ray diffraction patterns were obtained by methods known in the art using a Philips X-ray powder diffractometer, Goniometer model 1050/70 at a scanning speed of 2° per minute, with a Cu radiation of $\lambda = 1.5418$ Å.

The differential scanning calorimeter thermograms were obtained by methods known in the art using a DSC Mettler 821 Star°. The weight of the samples was less than 5 mg. The temperature range of scans was 30°C-300°C at a rate of 10°C/min. Samples were

purged with nitrogen gas at a flow rate of 40 mL/min. Standard 40 μl aluminum crucibles were used having lids with three small holes.

The infrared spectra were obtained by methods known in the art using a Perkin Elmer FT-IR Paragon 1000 spectrometer. Samples were analyzed in Nujol mulls. Spectra were obtained at 4 cm^{-1} resolution and 16 scans each.

Pharmaceutical Compositions Containing Sertraline Hydrochloride Polymorphs

In accordance with the present invention, these new crystalline forms of sertraline hydrochloride and known forms of sertraline hydrochloride prepared by the new methods disclosed herein may be prepared as pharmaceutical compositions that are particularly useful for the treatment of depression, obsessive-compulsive disorder and panic disorder. Such compositions comprise one of the new crystalline forms of sertraline hydrochloride with pharmaceutically acceptable carriers and/or excipients known to one of skill in the art.

For example, these compositions may be prepared as medicaments to be administered orally, parenterally, rectally, transdermally, bucally, or nasally. Suitable forms for oral administration include tablets, compressed or coated pills, dragees, sachets, hard or gelatin capsules, sub-lingual tablets, syrups and suspensions. Suitable forms of parenteral administration include an aqueous or non-aqueous solution or emulsion, while for rectal administration suitable forms for administration include suppositories with hydrophilic or hydrophobic vehicle. For topical administration the invention provides suitable transdermal delivery systems known in the art, and for nasal delivery there are provided suitable aerosol delivery systems known in the art.

Pharmaceutical compositions of the present invention contain sertraline hydrochloride Forms II, III, and V to X, optionally in mixture with other forms or amorphous sertraline. In addition to the active ingredient(s), the pharmaceutical compositions of the present invention may contain one or more excipients. Excipients are added to the composition for a variety of purposes.

Diluents increase the bulk of a solid pharmaceutical composition and may make a pharmaceutical dosage form containing the composition easier for the patient and care giver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g. Avicel®), microfine cellulose, lactose, starch, pregelitinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate

dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g. Eudragit®), potassium chloride, powdered cellulose, sodium chloride, sorbitol and talc.

Solid pharmaceutical compositions that are compacted into a dosage form like a tablet may include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions include acacia, alginic acid, carbomer (e.g. carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel®), hydroxypropyl methyl cellulose (e.g. Methocel®), liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon®, Plasdone®), pregelatinized starch, sodium alginate and starch.

The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach may be increased by the addition of a disintegrant to the composition. Disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium (e.g. Ac-Di-Sol®, Primellose®), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon®, Polyplasdone®), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab®) and starch.

Glidants can be added to improve the flowability of non-compacted solid composition and improve the accuracy of dosing. Excipients that may function as glidants include colloidal silicon dixoide, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

When a dosage form such as a tablet is made by compaction of a powdered composition, the composition is subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and dye, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease release of the product form the dye. Lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable

oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that may be included in the composition of the present invention include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol, and tartaric acid.

Solid and liquid compositions may also be dyed using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

In liquid pharmaceutical compositions of the present invention, the sertraline Forms and any other solid excipients are dissolved or suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerin.

Liquid pharmaceutical compositions may contain emulsifying agents to disperse uniformly throughout the composition an active ingredient or other excipient that is not soluble in the liquid carrier. Emulsifying agents that may be useful in liquid compositions of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol and cetyl alcohol.

Liquid pharmaceutical compositions of the present invention may also contain a viscosity enhancing agent to improve the mouth-feel of the product and/or coat the lining of the gastrointestinal tract. Such agents include acacia, alginic acid bentonite, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth and xanthan gum.

Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol and invert sugar may be added to improve the taste.

Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxy toluene, butylated hydroxyanisole and ethylenediamine tetraacetic acid may be added at levels safe for ingestion to improve storage stability.

A liquid composition according to the present invention may also contain a buffer such as guconic acid, lactic acid, citric acid or acetic acid, sodium guconate, sodium lactate, sodium citrate or sodium acetate.

Selection of excipients and the amounts to use may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

The solid compositions of the present invention include powders, granulates, aggregates and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable route in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts.

Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories, sachets, troches and losenges as well as liquid syrups, suspensions and elixirs.

An dosage form of the present invention is a capsule containing the composition, preferably a powdered or granulated solid composition of the invention, within either a hard or soft shell. The shell may be made from gelatin and optionally contain a plasticizer such as glycerin and sorbitol, and an opacifying agent or colorant.

The active ingredient and excipients may be formulated into compositions and dosage forms according to methods known in the art.

A composition for tableting or capsule filing may be prepared by wet granulation. In wet granulation some or all of the active ingredients and excipients in powder form are blended and then further mixed in the presence of a liquid, typically water, that causes the powders to clump up into granules. The granulate is screened and/or milled, dried and then screened and/or milled to the desired particle size. The granulate may then be tableted or other excipients may be added prior to tableting such as a glidant and or lubricant.

A tableting composition may be prepared conventionally by dry blending. For instance, the blended composition of the actives and excipients may be compacted into a

slug or a sheet and then comminuted into compacted granules. The compacted granules may be compressed subsequently into a tablet.

As an alternative to dry granulation, a blended composition may be compressed directly into a compacted dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Excipients that are particularly well suited to direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with experience and skill in particular formulation challenges of direct compression tableting.

A capsule filling of the present invention may comprise any of the aforementioned blends and granulates that were described with reference to tableting, only they are not subjected to a final tableting step.

Capsules, tablets and lozenges and other unit dosage forms preferably contain a dosage level of about 20, 25, 50 or 100 mg of equivalent base.

EXAMPLES

The present invention will now be further explained in the following examples. However, the present invention should not be construed as limited thereby. One of ordinary skill in the art will understand how to vary the exemplified preparations to obtain the desired results.

Example 1
Preparation of Sertraline Base

Sertraline mandelate was prepared according to procedures in U.S. Patent No. 5,248,699. Sertraline mandelate (5 g) was stirred at room temperature with 50 mL ethyl acetate. Aqueous sodium hydroxide was added dropwise until the sertraline mandelate was completely neutralized. The phases were separated and the organic phase was dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure resulting in sertraline base as an oil (3.2 g).

Example 2

Preparation of Sertraline Hydrochloride Ethanolate Form VI by Reslurry of Form I

Sertraline hydrochloride Form I (1 g) and absolute ethanol (20 mL) were stirred at room temperature for 24 hours. Filtration of the mixture yielded sertraline hydrochloride ethanolate Form VI.

Example 3

Preparation of Sertraline Hydrochloride Ethanolate Form VI by Reslurry of Form V

Sertraline hydrochloride Form V (1 g) and ethanol absolute (20 mL) were stirred at room temperature for 24 hrs. Filtration of the mixture yielded sertraline hydrochloride ethanolate Form VI.

Example 4

Preparation of Sertraline Hydrochloride Form II

Sertraline base (3 g) was dissolved in acetone (10 mL). Isopropanol containing hydrogen chloride (20 mL) was added to the solution until the pH is ~2. The stirring was continued overnight at room temperature. The resulting solid was filtered, washed with acetone and dried to yield sertraline hydrochloride Form II (2.61 g, yield 77.6%).

Example 5

Preparation of Sertraline Hydrochloride Form II in n-Butanol

HCl (g) was bubbled through a solution of sertraline base (33 g) in n-butanol (264 mL). The temperature rose to about 45°C. A gel-like solid was formed. The addition of HCl (g) was continued until pH 0.5 was reached. Then the stirring was continued at room temperature for 2.5 h. During the stirring the solid became a fine crystalline solid. The solid was filtered, washed with n-butanol (2 x 10 mL) and dried at 80°C for 24 h. The product is sertraline hydrochloride Form II. The x-ray powder diffraction spectrum obtained is Figure 3.

Example 6

Preparation of Sertraline Hydrochloride Form II

Sertraline hydrochloride Form V (10 g) was suspended in dimethylformamide (DMF) (30 mL). Heating was started and at about 70°C a clear solution is obtained. The solution was cooled to room temperature and the solid was filtered. After drying at 80°C for 24

hrs., sertraline hydrochloride Form II was obtained (6.6 g, yield 66%).

Example 7
Preparation of Sertraline Hydrochloride Form II by Granulation of Form V

Sertraline hydrochloride Form V (2 g) and absolute ethanol (0.5 mL) were stirred in a rotavapor at room temperature for 2 days. At the end of two days, the material contained sertraline hydrochloride Form II.

Example 8
Preparation of Sertraline Hydrochloride Form II from Form VI

A slurry of sertraline hydrochloride Form VI (50 g) and t-butyl-methyl ether (150 mL) were heated to reflux and the reflux was continued for 1 hour. The slurry was then allowed to cool to room temperature and filtered. The solid was washed with t-butyl-methyl ether (50 mL) and dried in a reactor under vacuum of 30 mm Hg with stirring. The dried solid so obtained is sertraline hydrochloride Form II (38.26 g: yield 86.7 %).

Example 9
Preparation of Sertraline Hydrochloride Form II from Form VI

Sertraline hydrochloride Form VI (25 g) was stirred with acetone (250 mL) at room temperature for 2 hours. The solid material was filtered and washed twice with acetone (25 mL). The wet solid was dried in a vacuum agitated drier to afford sertraline hydrochloride Form II (20.09 g: yield 98.6 %).

Example 10
Preparation of Sertraline Hydrochloride Form II and Sertraline Hydrochloride Form V by Drying Form VI

Sertraline hydrochloride ethanolate Form VI was dried at 105°C under vacuum (< 10 mm Hg) over 24 hours. The resulting dried material was sertraline hydrochloride Form II mixed with sertraline hydrochloride Form V.

Example 11
Preparation of Sertraline Hydrochloride Form II from Sertraline Mandelate in n-Butanol

Sertraline mandelate (20 g) and n-butanol were stirred at room temperature. The mixture was acidified with hydrogen chloride until pH 0 was reached. During the acidification the temperature of the reaction mixture rose to ~50°C. After the natural

cooling to room temperature, the mixture was stirred at room temperature for two hours. The solid was filtrated, washed with n-butanol and dried at 80°C to afford sertraline hydrochloride Form II (9.02 g).

Example 12

Preparation of Sertraline Hydrochloride Form II from Sertraline Hydrochloride Form VIII

Sertraline hydrochloride Form VIII (13 g) was heated in acetone (130 mL) at reflux for 1 hour. The slurry was than cooled to room temperature and the solid was filtrated and washed with acetone (2x10 mL). After drying sertraline hydrochloride Form II was obtained (7.9 g).

Example 13

An aqueous sodium hydroxide solution, 10 %, was added drop-wise to a slurry of sertraline mandelate crystals (10 g) in ethyl acetate (650 mL), until complete dissolution was obtained (25 mL). After separation of the phases, the organic phase was washed with water (300 mL) and then dried with $MgSO_4$. The organic solution was diluted with ether (690 mL) and gaseous hydrochloric acid was bubbled through the solution until pH 1.3 was reached. The addition of hydrogen chloride resulted in a temperature increase to about 30°C. The resulting slurry of sertraline was stirred at room temperature overnight. The solid was then isolated by filtration, washed twice with ether (2 x 20 mL) and air dried. The dried solid, sertraline hydrochloride, was not sertraline hydrochloride Form II, as shown in Figure 1.

Example 14

An aqueous sodium hydroxide solution, 10 %, was added drop-wise to a slurry of sertraline mandelate crystals (15 g) in ethyl acetate (810 mL), until complete dissolution was obtained (35 mL). The organic and aqueous phases were separated and, the organic phase was dried over $MgSO_4$. The organic solution was then diluted with ether (820 mL) and gaseous hydrogen chloride (2.36 g, 2 eq.) was bubbled through the solution until pH 1.5 was reached. The temperature was about 25°C. The slurry was stirred at room temperature overnight. The solid was filtrated, washed with ether (2 x 15 mL) and air-dried. The dried solid, sertraline hydrochloride, was not sertraline hydrochloride Form II.

Example 15

An aqueous sodium hydroxide solution, 10 %, was added drop-wise to a slurry of sertraline mandelate crystals (15 g) in ethyl acetate (810 mL), until complete dissolution was obtained. The organic and aqueous phases were separated and the organic phase was dried over $MgSO_4$ and diluted with an equal volume of ether (820 mL). Gaseous hydrochloric acid (4.82 g) was bubbled through the solution until pH 1 was reached. The slurry was stirred at room temperature overnight. The solid was filtrated, washed with ether (2 x 15 mL) and air-dried. The dried solid, sertraline hydrochloride, was not sertraline hydrochloride Form II.

Example 16

An aqueous sodium hydroxide solution, 10 %, was added drop-wise to a slurry of sertraline mandelate crystals (15 g) in ethyl acetate (810 mL), until complete dissolution is obtained. The phases were separated and the organic phase was dried over $MgSO_4$ and diluted with an equal volume of ether (820 mL). Gaseous hydrogen chloride was slowly bubbled through the solution (over about 3 hours) until pH 1.5 was reached. The slurry was stirred at room temperature over night. The dried solid, sertraline hydrochloride, was not sertraline hydrochloride Form II.

Example 17
Preparation of Sertraline Hydrochloride Form VIII

Sertraline base (2.7 g) was suspended in 27 mL of water. This mixture was heated to 80°C and treated with hydrochloric acid until about pH 1 was reached. A clear solution was obtained which on cooling gave a precipitate. After 2 hours stirring at room temperature the solid was isolated by filtration. This solid was characterized by powder x-ray diffraction and found to be sertraline hydrochloride Form VIII.

Example 18
Preparation of Sertraline Hydrochloride Form VIII

Sertraline hydrochloride ethanolate (Form VI) (40 g) was stirred with water (80 mL) for 1 hour at room temperature. The slurry was filtrated and washed with water to yield sertraline hydrochloride hydrate Form VIII.

Example 19
Preparation of Sertraline Hydrochloride Form VII

Sertraline hydrochloride Form V (1.003 g) was stirred for 24 hours at room

temperature in 20 mL water (HPLC grade). At the end of the stirring the mixture looked like a jelly suspension. The suspension was filtrated and the compound obtained was kept at cold conditions (4°C) until analyzed by x-ray diffraction, which determined the compound to be sertraline hydrochloride Form VII.

Example 20

Preparation of Sertraline Hydrochloride Form VI and Form V

Sertraline base (25 g) was dissolved in methanol (125 mL) at room temperature. The solution was acidified with hydrogen chloride gas until pH 1.5 was reached. (Precipitation occurred during acidification.) The temperature rose to approximately 40°C. The slurry was allowed to cool to room temperature and stirred for about 2 hours. The solid was separated by filtration to give sertraline hydrochloride methanolate Form VI. Drying the product overnight gave sertraline hydrochloride Form V.

Example 21

Preparation of Sertraline Hydrochloride Form VI and Form V

Sertraline base (3.2 g) was dissolved in absolute ethanol (32 mL) at room temperature and then hydrogen chloride gas was bubbled in until pH 0.5 was reached. The temperature rose to 40°C. The slurry was allowed to cool to room temperature and stirred for about 16 hours. The solid was separated by filtration, and washed with ethanol (3 x 2 mL). Figure 5 sets forth the X-ray diffraction pattern of the product (sertraline hydrochloride ethanolate Form VI) so obtained. Drying overnight at 50-60°C of that product yielded 2.95 g (82%) of sertraline hydrochloride Form V.

Example 22

Preparation of Sertraline Hydrochloride Form V

Sertraline base (3 g) was dissolved in absolute ethanol (15 mL) at room temperature. A saturated solution of hydrogen chloride in isopropyl alcohol was added dropwise to reach a pH of 1.3. The resulting slurry was stirred at room temperature overnight. The solid was separated by filtration and dried overnight at 50-60°C yielding 2.75 g (81. 8%) sertraline hydrochloride Form V.

Example 23

Preparation of Sertraline Hydrochloride Form V

Sertraline base (3 g) was dissolved in absolute ethanol (15.5 mL) at room temperature and then the solution was cooled to approximately 0°C. Hydrogen chloride gas was

bubbled until pH 0.5 was reached. The temperature rose to approximately 7°C. Precipitation occurred and the slurry was stirred at about 10°C for 2 hours. The solid was isolated by filtration, washed with ethanol and dried at approximately 50°C. The dried material (2.87 g, yield 82.7%) was sertraline hydrochloride Form V.

Example 24
Preparation of Sertraline Hydrochloride Form V

Sertraline base (3 g) was stirred with 35 mL water. The slurry was heated at ~70°C and, while maintaining this temperature, concentrated hydrochloric acid was added until pH 1 was reached. During acidification, almost complete dissolution was observed followed by precipitation. The mixture was cooled to room temperature and stirred for 2 hours. The solid was isolated by filtration, washed with water and dried overnight at 50-60° C, yielding 3.23 g (96%) sertraline hydrochloride Form V.

Example 25
Preparation of Sertraline Hydrochloride Form V

Sertraline base (3 g) was dissolved in 10 mL absolute ethanol at 40°C. The solution was heated to 50°-60°C and concentrated hydrochloric acid 32% (1.2 mL) was added until pH ~1.3 was reached. Water (12 mL) was added. The resulting clear solution was concentrated to half its volume and was allowed to cool naturally to room temperature. The solid was isolated by filtration, washed with water and dried overnight at 50-60°C, yielding 3.18 g (94.65%) sertraline hydrochloride Form V.

Example 26
Preparation of Sertraline Hydrochloride Form V

Sertraline base (3.7 g) was dissolved in 18.5 mL absolute ethanol and the solution was heated to 60°C. Hydrogen chloride gas was bubbled through the ethanol solution until pH ~0.5 was reached. The mixture was cooled to room temperature and the stirring was continued for 2 hours. The solid obtained after filtration, washing with ethanol and drying at 50° C was sertraline hydrochloride Form V (3.16 g, yield 76%).

Example 27
Preparation of Sertraline Hydrochloride Form V

Sertraline free base was dissolved in ethanol absolute and the solution was acidified with hydrogen chloride gas to about pH 3. Precipitation occurs and the slurry was stirred at room temperature for 2 hours. The resulting solid was filtered, washed with ethanol and

dried to yield sertraline hydrochloride Form V.

Example 28
Preparation of Sertraline Hydrochloride Form V

Sertraline free base (13.3 g) was dissolved in absolute ethanol (60 mL) and was added dropwise over one hour to ethanol (20 mL) containing hydrogen chloride (17.5 g) at 35°C with precipitation. After 2 hours, the solid was filtrated, washed with ethanol and dried at about 80° C to yield sertraline hydrochloride Form V (12.9 g, yield 87%).

Example 29
Preparation of Sertraline Hydrochloride Form V

Anhydrous sertraline hydrochloride (2 g) was stirred with 14 mL absolute ethanol and heated to reflux to obtain a clear solution. The solution was seeded with sertraline hydrochloride Form V and cooled naturally to room temperature. Massive precipitation was observed at about 50°C. The slurry was stirred at room temperature during 2 hours. The solid was filtered, washed with ethanol (3 mL) and dried overnight at 50-60°C yielding 1.71 g (85.5%) of sertraline hydrochloride Form V.

Example 30
Preparation of Sertraline Hydrochloride Form V

Sertraline hydrochloride ethanolate (Form VI) (40 g) in 400 mL water was heated to 80°C and complete dissolution was obtained. The pH was adjusted to approximately one with hydrochloric acid and the solution was naturally cooled to room temperature and stirred for 2 hours. The solid was filtered and dried at 50°C for approximately 16 hours, yielding sertraline hydrochloride Form V.

Example 31
Preparation of Sertraline Hydrochloride Form V

Sertraline hydrochloride ethanolate (Form VI) (2 g) was mechanically stirred with ethanol (0.5 mL) at room temperature for 40 hours. The resulting solid was sertraline hydrochloride Form V.

Table 1 sets forth a summary of additional experiments conducted generally following procedures described above.

TABLE 1 PREPARATION OF SERTRALINE HCL - FORM V

SERTRALINE BASE AS STARTING MATERIAL

Exp't	Method of Crystallization	XRD	Yield (%)
A	Methanol/HCl gas	V	78.7
B	Methanol/HCl gas	V	69
C	Methanol/HCl aqueous	V	87.8
D	Ethanol/HCl gas	V	80.9
E	Water/HCl aqueous	V	96
F	Hexane/Isopropyl alcohol/HCl gas	V	89.9
G	Methanol/HCl aqueous/water	V	89
H	Isopropyl alcohol/HCl aqueous/water	V	78
I	Ethanol/HCl aqueous/evaporation of ethanol	V	96.1
J	Ethyl acetate/HCl aqueous/water/evaporation of ethyl acetate	V	96.1
K	Ethanol/isopropyl alcohol/HCl gas	V	81.8
L	Methanol/isopropyl alcohol/HCl gas	V	82.4
	SERTRALINE HCl AS STARTING MATERIAL		
M	Methanol (Form I and amorphous)	V	60
N	Ethanol (Form V)	V	85.5
O	Isopropyl alcohol/water (Form V)	V	28

PXRD = powder x-ray diffraction.

Example 32

Preparation of Sertraline Hydrochloride Form VII

1.003 g Sertraline hydrochloride Form V was stirred for 24 hours at room temperature in 20 mL water (HPLC grade). At the end of the stirring the mixture looked like a jelly suspension. The suspension was filtrated and the compound obtained was kept at cold conditions (4°C) until analyzed by x-ray diffraction.

Example 33

Preparation of Sertraline Hydrochloride Form VII from Sertraline Hydrochloride Form VI

A solution of sertraline hydrochloride ethanolate (Form VI) (40 g) in water (400 mL) was heated at 80°C and complete dissolution of sertraline hydrochloride ethanolate (Form

VI) was obtained. The pH was adjusted to about 1 and the solution was allowed to cool to room temperature and then stirred for 2 additional hours. The solid was isolated by filtration and washed with water to yield sertraline hydrochloride Form VII.

Sertraline hydrochloride Form VII dried overnight at 80°C forms sertraline hydrochloride Form V.

Example 34
Preparation of Sertraline Hydrochloride Forms VIII and IX from Sertraline Base

Sertraline base (2.7 g) was suspended in 27 mL of water. This mixture was heated to 80°C and treated with hydrochloric acid until about pH 1 was reached. A clear solution was obtained, which on cooling gave a precipitate. After 2 hours stirring at room temperature the solid was isolated by filtration. This solid was characterized by powder x-ray diffraction (see Figure 3, Form VIII). Drying for 24 hours at ~50°C yielded 2.32 g (76.8%) of sertraline hydrochloride Form IX, characterized by powder x-ray diffraction, infra-red absorption, differential scanning calorimetry, and thermal gravimetric analysis as set forth above and depicted in Figures 8, 10, and 12.

Example 35
Preparation of Sertraline Hydrochloride Form VIII from Sertraline Hydrochloride Form II

Sertraline hydrochloride Form II (0.4 g) and water (8 mL) were stirred at room temperature over night. The solid was filtrated to yield sertraline hydrochloride hydrate Form VIII.

Example 36
Preparation of Sertraline Hydrochloride Form X

In a 0.1 liter three-necked bottom round flask equipped with a mechanical stirrer, a condenser and a thermometer, 30 mL benzyl alcohol is added to 10 g sertraline hydrochloride. The suspension is heated to 100°C when a clear solution is obtained. The solution is cooled 2 hours to 25°C and the precipitate is filtered and washed with benzyl alcohol. After drying under vacuum at 80°C for 24 hours, 6.2 g of sertraline hydrochloride Form X is obtained (yield 62%). The sertraline hydrochloride Form X was characterized by powder x-ray diffraction and infrared absorption analysis as set forth above and in Figure 14 and Figure 15.

Example 37

Preparation of Sertraline Hydrochloride Ethanolate Form VI by Reslurry of Form II

Sertraline hydrochloride Form II (1 g) and absolute ethanol (20 mL) were stirred at room temperature for 24 hours. Filtration of the mixture yielded sertraline hydrochloride ethanolate Form VI .

Example 38

Preparation of Amorphous Sertraline Hydrochloride

Sertraline free base (10 g) was dissolved in ethyl acetate (690 mL). At room temperature, ether (690 mL) was added to the sertraline ethyl acetate solution and the solution was acidified with HCl gas to about pH 0.5. The resulting gelatinous suspension was stirred at room temperature over night. Filtration and air drying of the suspension yielded amorphous sertraline hydrochloride (9.39 g, yield 83.8%).

Example 39

Preparation of Sertraline Hydrochloride Form III from Form V

Sertraline hydrochloride Form V was heated at 150° C in a reactor under mechanical stirring for 24 hrs. The resulting material obtained was sertraline hydrochloride Form III.

Example 40

Preparation of Sertraline Hydrochloride Form III from Form VI

Sertraline hydrochloride form VI was heated to 180° C for 24 hours. The dried material is sertraline hydrochloride Form III.

Example 41

Preparation of Sertraline Hydrochloride Form III from Form V

Sertraline hydrochloride Form V was heated at a temperature ≥ 180° C for 24 hours. The resulting material was sertraline hydrochloride Form III.

Example 42

Preparation of Amorphous Sertraline Hydrochloride

Sertraline hydrochloride Form V (10 g) was dissolved in water (2L) and this solution was dried by the spray dryer technique. The material obtained in this way is Sertraline hydrochloride amorphous.

Example 43

Preparation of Amorphous Sertraline Hydrochloride by Sublimation

Sertraline hydrochloride Form I was sublimated at 190-200°C, at a vacuum of 30-0.1 mm Hg, using a laboratory-type sublimator. The resulting material was amorphous sertraline hydrochloride.

A similar procedure starting from Form V also gave amorphous sertraline hydrochloride.

Example 44

Preparation of Sertraline Hydrochloride Form V from Amorphous Sertraline Hydrochloride

Sertraline hydrochloride amorphous was heated to 80°C for 24 hours. The resulting product was sertraline hydrochloride Form V.

It should be understood that some modification, alteration and substitution is anticipated and expected from those skilled in the art without departing from the teachings of the invention. Accordingly, it is appropriate that the following claims be construed broadly and in a manner consistent with the scope and spirit of the invention.

WHAT IS CLAIMED IS:

1. A process for making sertraline hydrochloride Form II comprising the steps of:
   (a) dissolving sertraline base or sertraline mandelate in an organic solvent to form a solution;
   (b) adding hydrogen chloride to the solution;
   (c) heating the solution to a temperature between about room temperature and about reflux for a time sufficient to induce the formation of sertraline hydrochloride Form II; and
   (d) isolating sertraline hydrochloride Form II.

2. The process of claim 1 wherein the solvent is selected form the group consisting of ethyl acetate, acetone, hexane, t-butyl-methyl ether, isopropyl alcohol, n-butanol, t-butanol, iso-butanol, and cyclohexane, and mixtures thereof.

3. The process of claim 2 wherein the preferred solvent is t-butyl-methyl ether.

4. The process of claim 2 wherein the preferred solvent is n-butanol.

5. The process of claim 1 wherein the hydrogen chloride is added as gaseous hydrogen chloride.

6. The process of claim 1 wherein the hydrogen chloride is added as a solution of hydrogen chloride.

7. The process of claim 6 wherein the solution of hydrogen chloride is selected from the group consisting of isopropyl alcohol and hydrogen chloride, acetone and hydrogen chloride, and n-butanol and hydrogen chloride.

8. The process of claim 1 wherein the solution is heated to the reflux temperature of the solvent.

9. Sertraline hydrochloride Form II made by the process of claim 1.

10. A process for making sertraline hydrochloride Form II comprising the steps of:
   (a) dissolving sertraline hydrochloride in a solvent selected from the group consisting of dimethylformamide, cyclohexanol, acetone and mixtures thereof;
   (b) heating the solution for a time sufficient to effect transformation to sertraline hydrochloride Form II; and
   (c) isolating sertraline hydrochloride Form II.

11. Sertraline hydrochloride Form II made by the process of claim 10.

12. A process for making sertraline hydrochloride Form II comprising the steps of:

(a) granulating sertraline hydrochloride Form V in ethanol or methanol; and

(b) stirring the mixture of sertraline hydrochloride Form V and ethanol or methanol for a time sufficient to induce transformation to sertraline hydrochloride Form II.

13. Sertraline hydrochloride Form II made by the process of claim 12.

14. A process for making a mixture of sertraline hydrochloride Form II and Form V comprising the steps of:

(a) heating sertraline hydrochloride ethanolate Form VI at up to 1 atmosphere pressure; and

(b) isolating a mixture of sertraline hydrochloride Form II and Form V.

15. A mixture of sertraline hydrochloride Form II and Form V made by the process of claim14.

16. A process for making sertraline hydrochloride Form II comprising the steps of:

(a) suspending a water or solvent adduct of sertraline hydrochloride in a solvent selected from the group consisting of acetone, t-butyl-methyl ether, cyclohexane, n-butanol, and ethyl acetate, such that a slurry is formed, for a time sufficient to effect transformation to sertraline hydrochloride Form II; and

(b) filtering the slurry to isolate sertraline hydrochloride Form II.

17. The process of claim 16 wherein the process takes place at a temperature between about 25°C and about 120°C.

18. The process of claim 16 wherein the process takes place under reflux conditions.

19. The process of claim 16 in which the sertraline hydrochloride is suspended in about 1 to about 10 volumes of organic solvent.

20. The process of claim 16 wherein the solvent is t-butyl-methyl-ether.

21. The process of claim 16 wherein the solvent is acetone.

22. The process of claim 16 wherein the solvent is ethyl acetate.

23. The process of claim 16 wherein the solvent is n-butanol.

24. The process of claim 16 wherein the sertraline hydrochloride water or solvate adduct is sertraline hydrochloride Form VI.

25. The process of claim 16 wherein the sertraline hydrochloride water or solvate adduct is sertraline hydrochloride Form VII.

26. The process of claim 16 wherein the sertraline hydrochloride water or solvate adduct is sertraline hydrochloride Form VIII.

27. Sertraline hydrochloride Form II made by the process of claim 16.

28. Sertraline hydrochloride Form II.

29. Sertraline hydrochloride characterized by an x-ray powder diffraction pattern comprising peaks at about 5.5, 11.0, 12.5, 13.2, 14.7, 16.4, 17.3, 18.1, 19.1, 20.5, 21.9, 22.8, 23.8, 24.5, 25.9, 27.5, and 28.0 degrees two theta.

30. A pharmaceutical composition for the treatment of depression comprising of the sertraline hydrochloride of claim 29 together with a pharmaceutically acceptable carrier.

31. A method for treating depression comprising the step of administering to a subject in need of such treatment a therapeutically effective amount of the pharmaceutical composition of claim 30.

32. A process for making sertraline hydrochloride Form V comprising the steps of:

(a) dissolving or suspending sertraline hydrochloride in a suitable solvent;

(b) removing the solvent; and

(c) drying to form sertraline hydrochloride Form V.

33. The process of claim 32, wherein the solvent is selected from the group consisting of methanol, ethanol, water, 1-methoxy-2-propanol, trichloroethane, and isopropyl alcohol, and mixtures thereof.

34. The process of claim 33, wherein the solvent is water.

35. The process of claim 34, wherein the step of drying to form sertraline hydrochloride Form V is achieved by spray drying.

36. The process of claim 32, further comprising the steps of seeding the solution with sertraline hydrochloride Form V.

37. A process for making sertraline hydrochloride Form V comprising the steps of:

(a) dissolving or suspending sertraline base in a solvent;

(b) adding hydrogen chloride to the solvent to reduce the pH of the solution or suspension; and

(c) isolating sertraline hydrochloride Form V from the solution or suspension.

38. The process of claim 37 wherein the pH of the solution or suspension of sertraline base and hydrogen chloride is about 0 to about 4.

39. The process of claim 37 wherein the solvent is selected from the group consisting of methanol, ethanol, water, ethyl acetate, isopropyl alcohol, ether, hexane, and toluene, and mixtures thereof.

40. The process of claim 39 wherein the solvent is ether.

41. The process of claim 39 wherein the solvent is water.

42. The process of claim 41 wherein the step of isolating sertraline hydrochloride Form V is done by spray drying the solution or suspension.

43. A process for making sertraline hydrochloride Form V comprising the step of drying sertraline hydrochloride Form VII.

44. A process for making sertraline hydrochloride Form V comprising the steps of:

(a) dissolving or suspending sertraline hydrochloride in water;

(b) adding a sufficient amount of hydrogen chloride to facilitate percipitation of sertraline hydrochloride;

(c) removing the water; and

(d) isolating sertraline hydrochloride Form V.

45. A process for making sertraline hydrochloride Form VI comprising the steps of:

(a) dissolving sertraline base in a solvent;

(b) adding hydrogen chloride to the solvent; and

(c) isolating sertraline hydrochloride Form VI without further drying.

46. The process of claim 45 wherein the isolation step comprises precipitation of sertraline hydrochloride Form VI followed by filtration.

47. The process of claim 45 wherein the solvent is at least one solvent selected from the group consisting of ethanol, methanol, or mixtures of methanol or ethanol with water.

48. A process for making sertraline hydrochloride Form VI comprising the steps of:

(a) dissolving or suspending sertraline hydrochloride in ethanol or methanol;

(b) stirring for a time sufficient to induce the transformation of sertraline hydrochloride to sertraline hydrochloride Form VI; and

(c) isolating sertraline hydrochloride Form VI.

49. A process for making sertraline hydrochloride Form VIII comprising the steps of:

(a) suspending sertraline base in water;

(b) adding hydrogen chloride to the water; and

(c) filtrating the precipitate so obtained without further drying.

50. A process for making sertraline hydrochloride Form VIII comprising the steps of:

(a) suspending or dissolving sertraline hydrochloride ethanolate Form VI or sertraline hydrochloride Form II in water or a mixture of water and isopropyl alcohol; and

(b) isolating sertraline hydrochloride Form VIII.

51. A process for making sertraline hydrochloride Form III comprising the steps of:

(a) heating sertraline hydrochloride Form V or Form VI to a temperature sufficient, and for a time sufficient, to induce the transformation of sertraline hydrochloride Form V or Form VI to sertraline hydrochloride Form III; and

(b) isolating sertraline hydrochloride Form III.

52. The process of claim 51 wherein the temperature is between about 150°C and about 180°C.

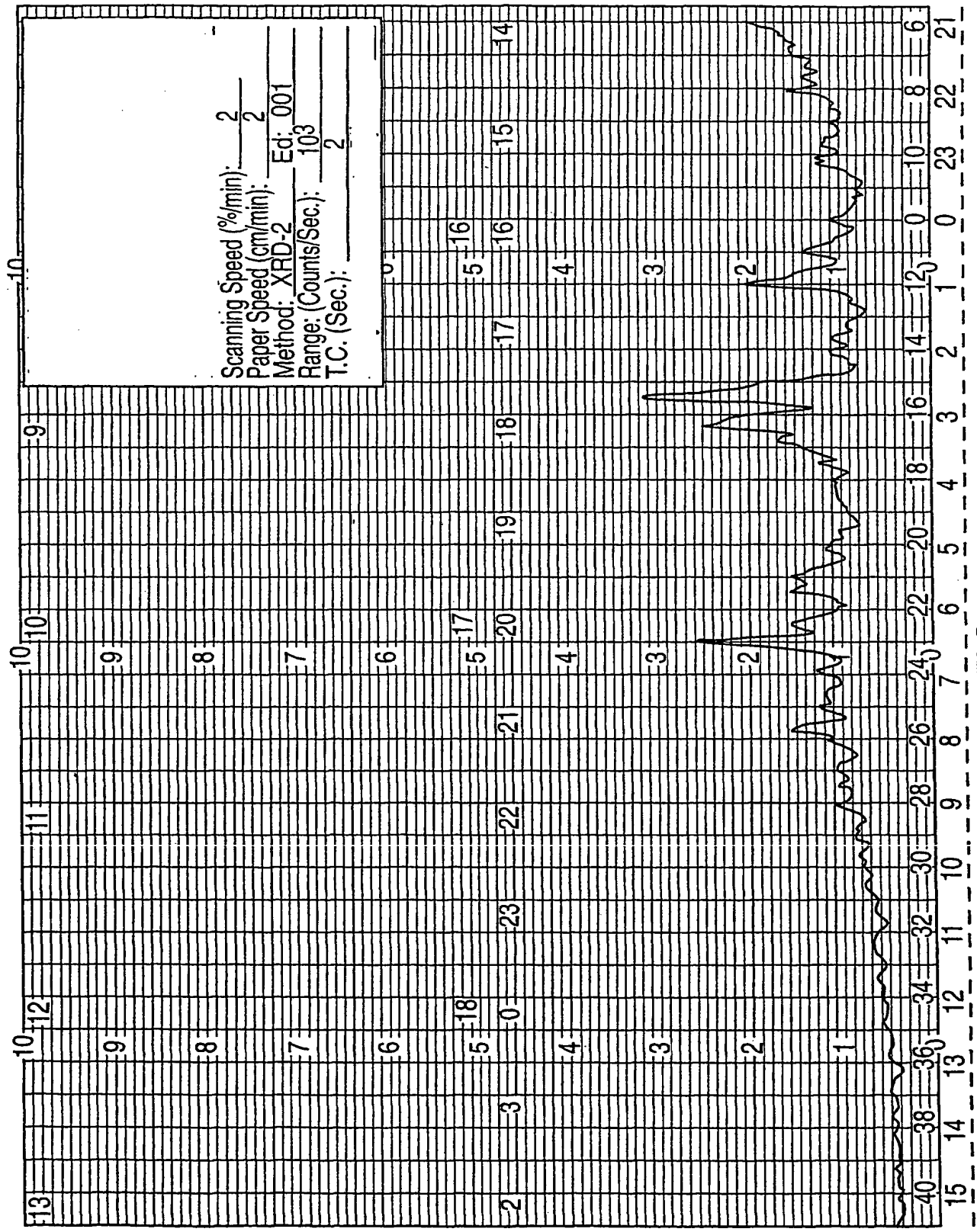
53. A process for making amorphous sertraline hydrochloride comprising the steps of:

(a) suspending or dissolving sertraline base in a non-polar organic solvent;

(b) adding gaseous hydrochloric acid; and

(c) and isolating amorphous sertraline hydrochloride.

54. The process of claim 53 wherein the solvent is selected from the group consisting of ether, toluene and t-butyl-methyl ether, and mixtures thereof.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Range: (Counts/Sec.): 103
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FIG. 1

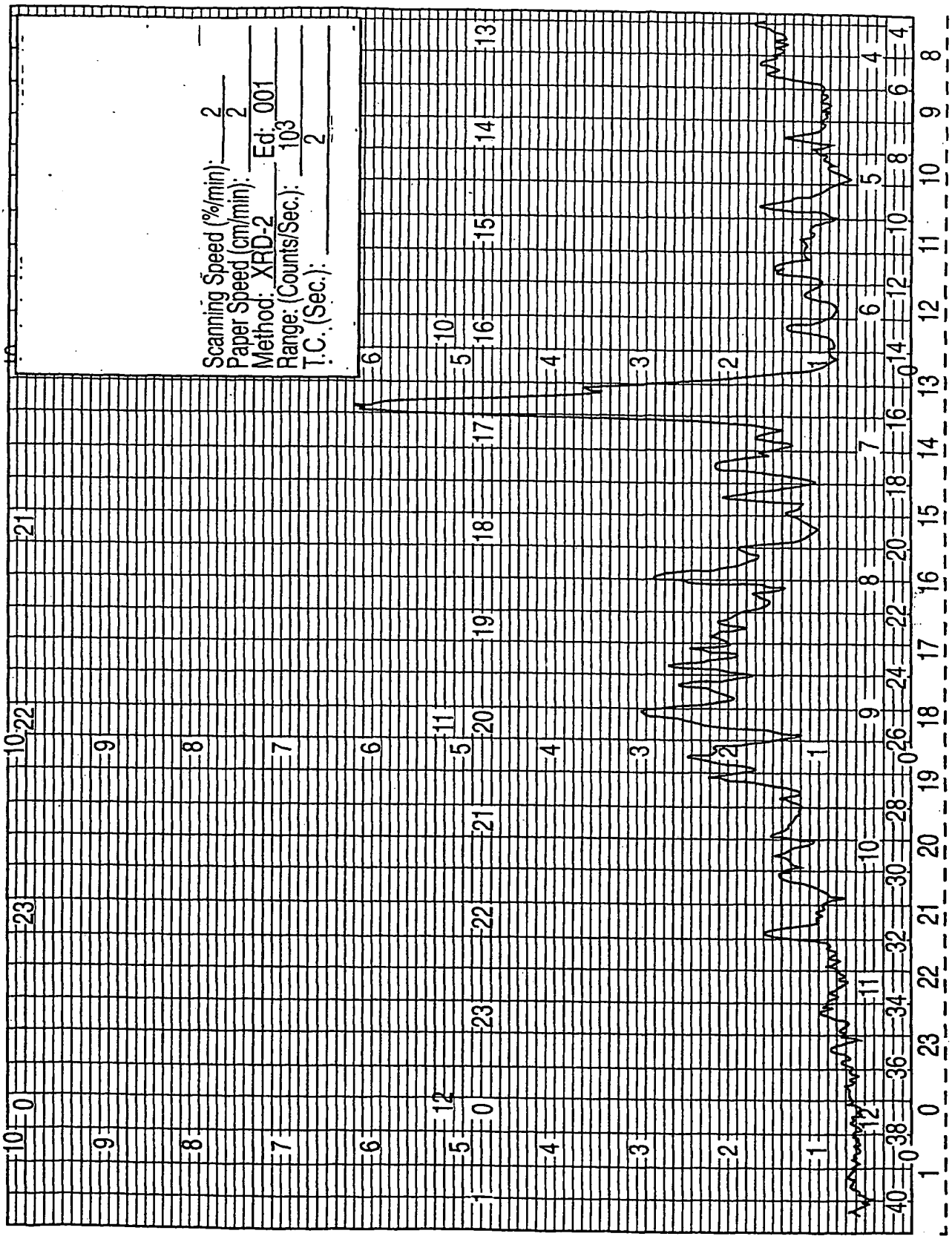
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FIG. 2

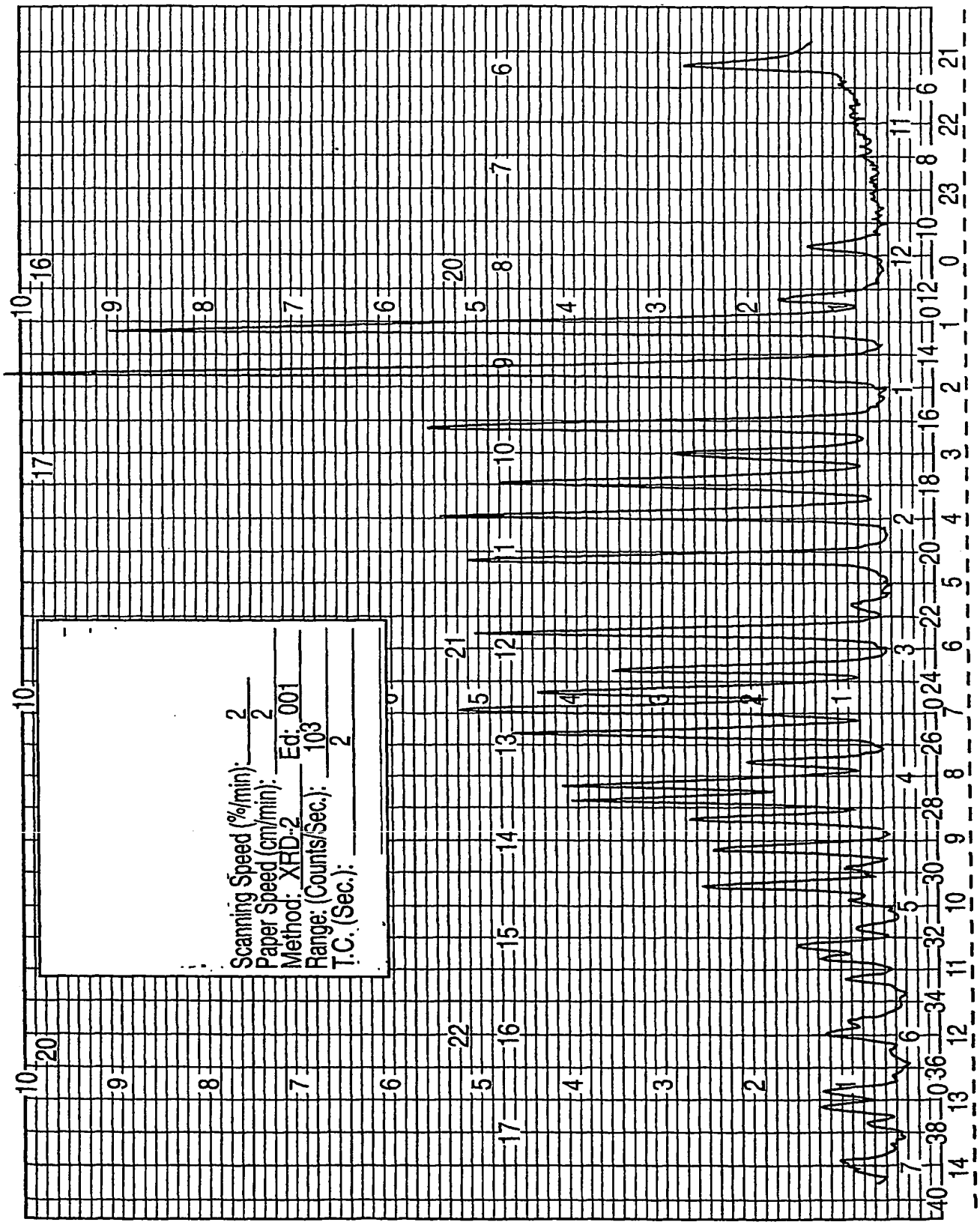
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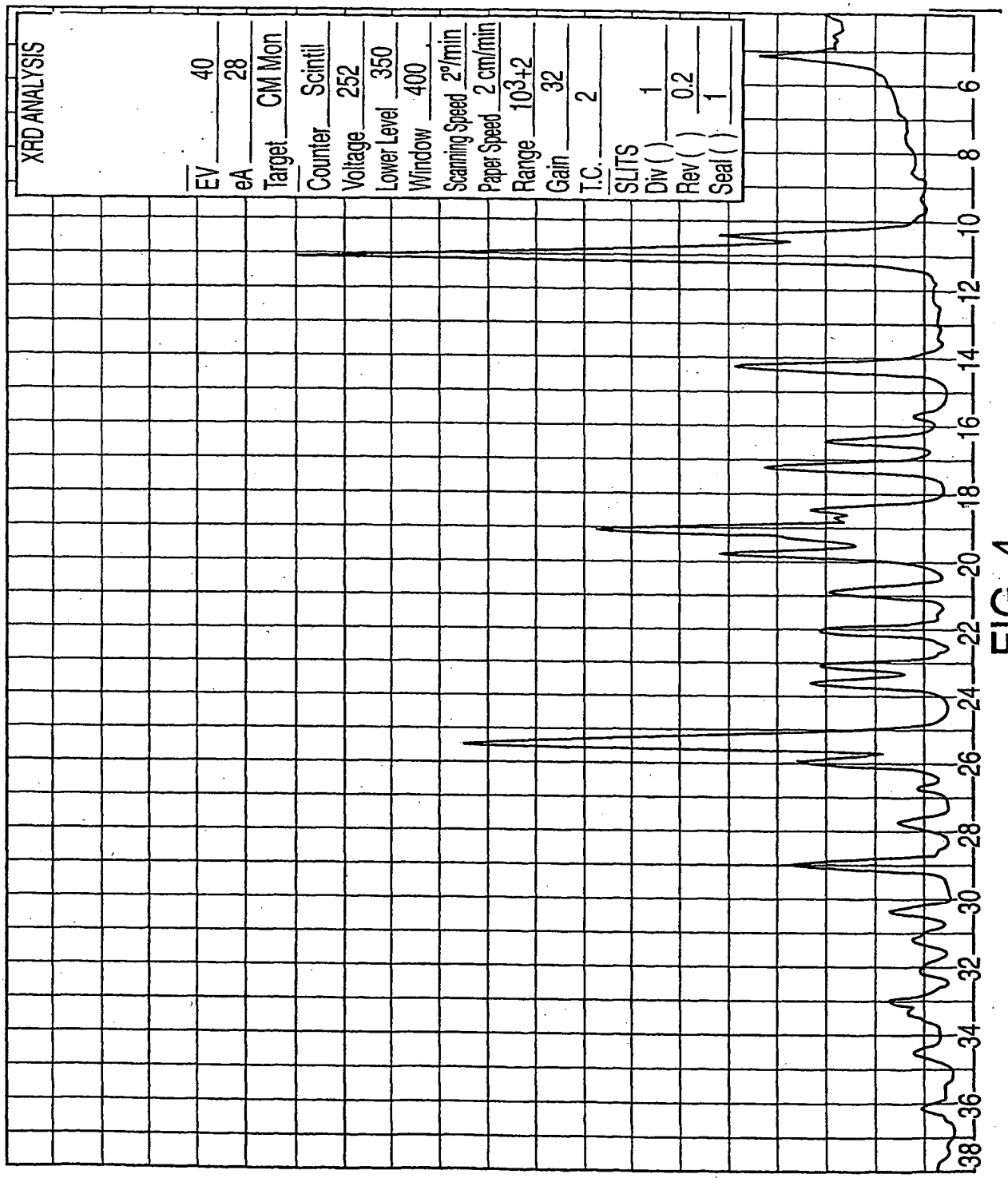
FIG. 3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Target CM Mon
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Lower Level 350
Window 400
Scanning Speed 2°/min
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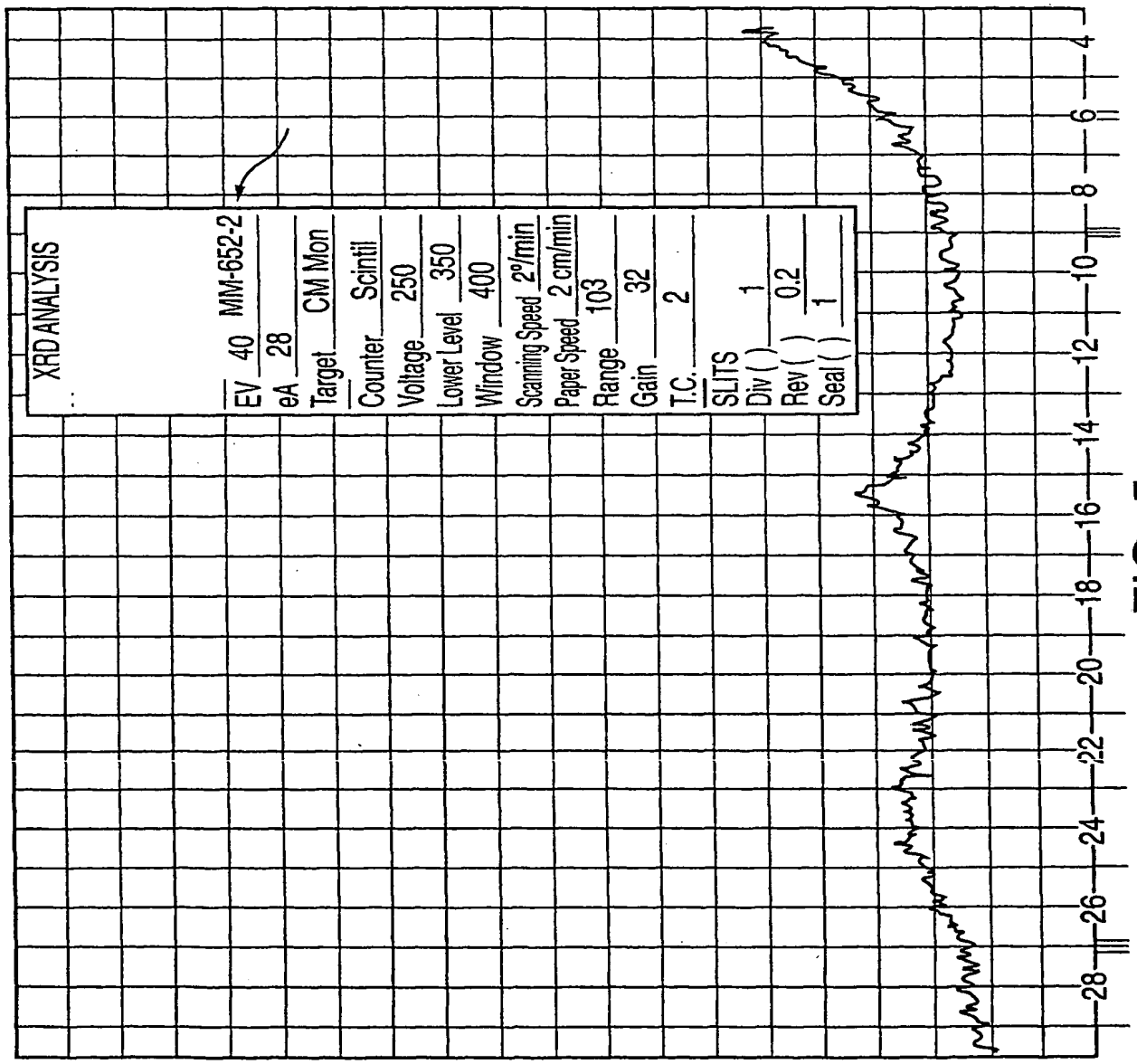
Range 10^3+2
Gain 32
T.C. 2
SLITS
Div ( ) 1
Rev ( ) 0.2
Seal ( ) 1
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38

FIG. 4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Range 10^3
Gain 32
T.C. 2
SLITS
Div ( ) 1
Rev ( ) 0.2
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26
28

FIG. 5

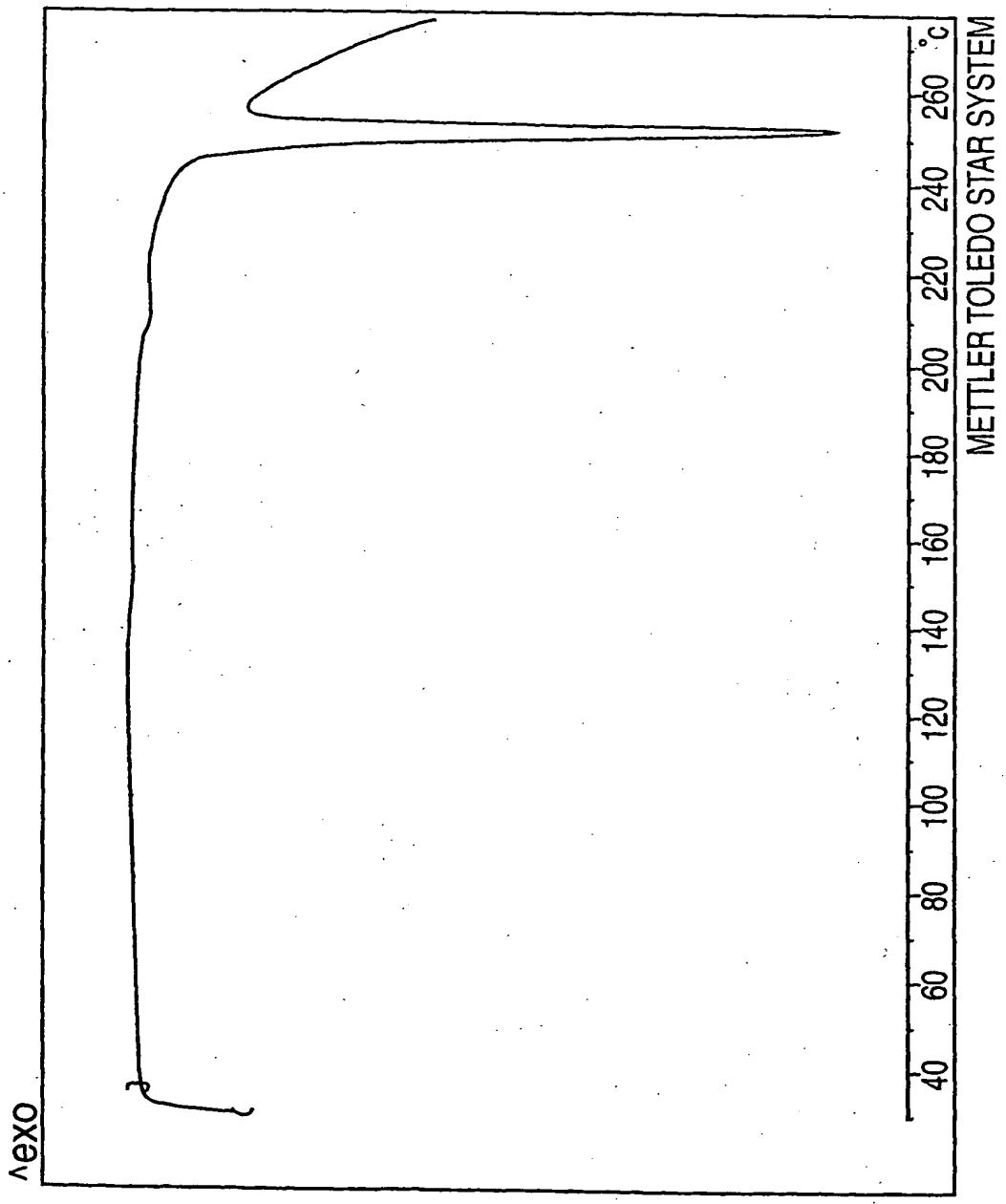

Exo
40
60
80
100
120
140
160
180
200
220
240
260
°C
METTLER TOLEDO STAR SYSTEM

FIG. 6

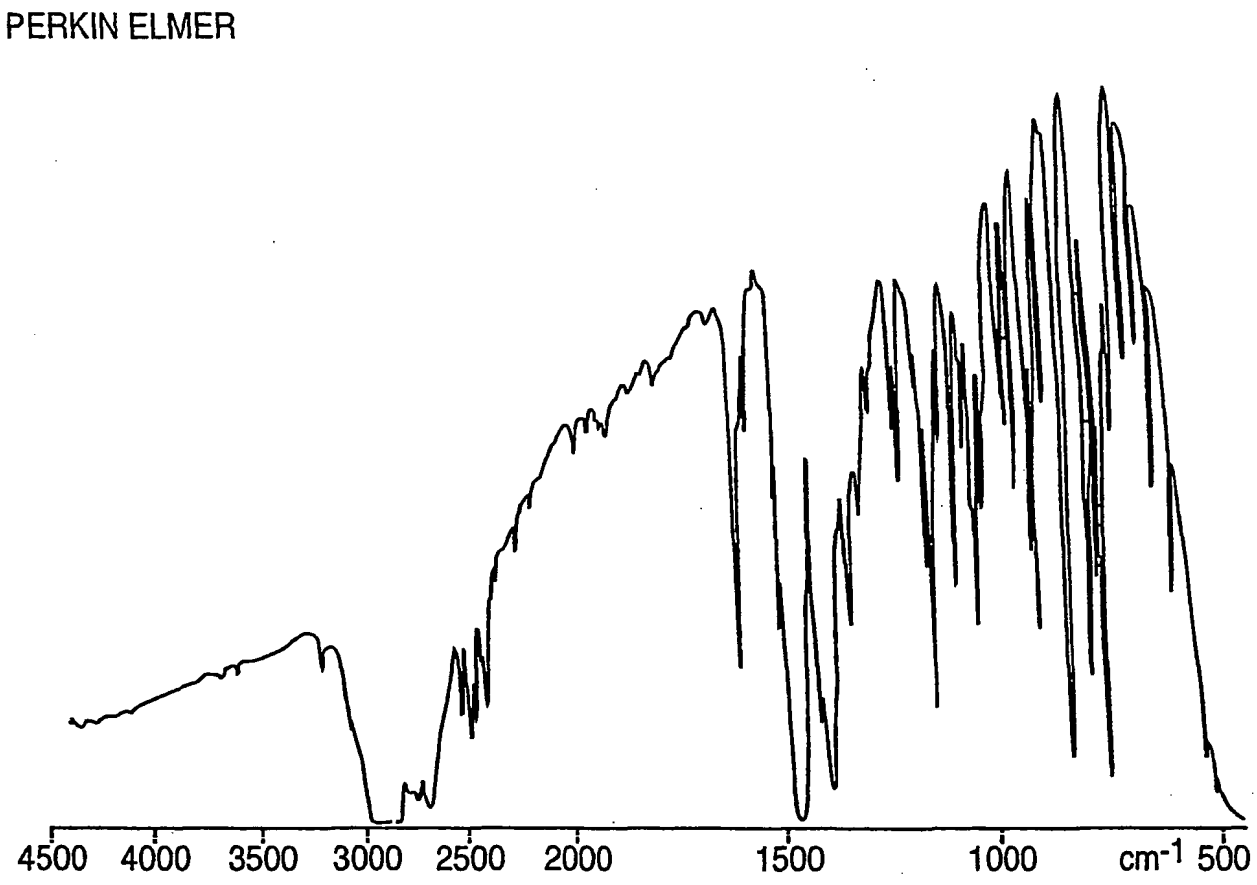

PERKIN ELMER
4500
4000
3500
3000
2500
2000
1500
1000
cm-1
500
16 SCANS, 4. 0cm-1
SERTRALINE HCL AL 9690

FIG. 7

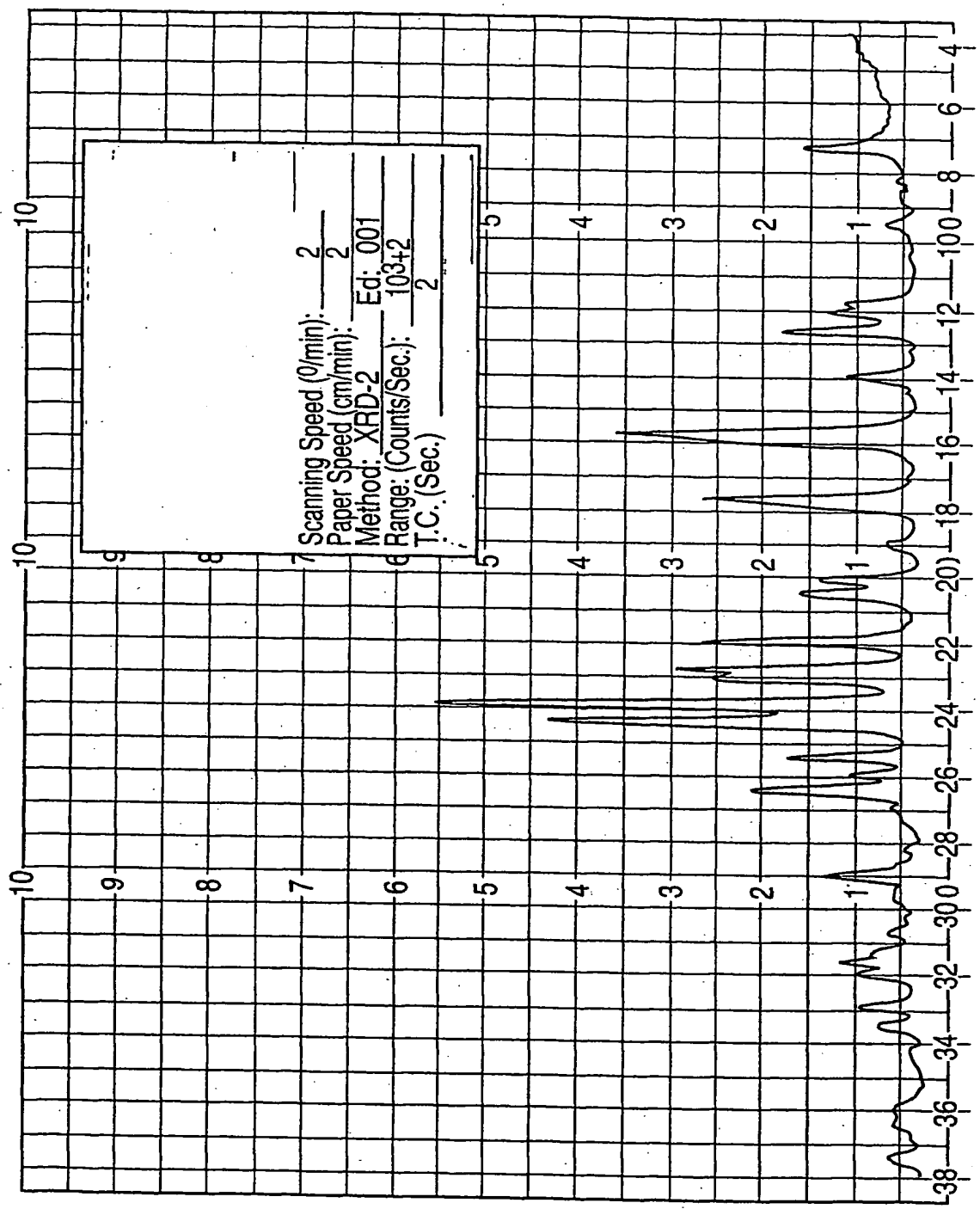
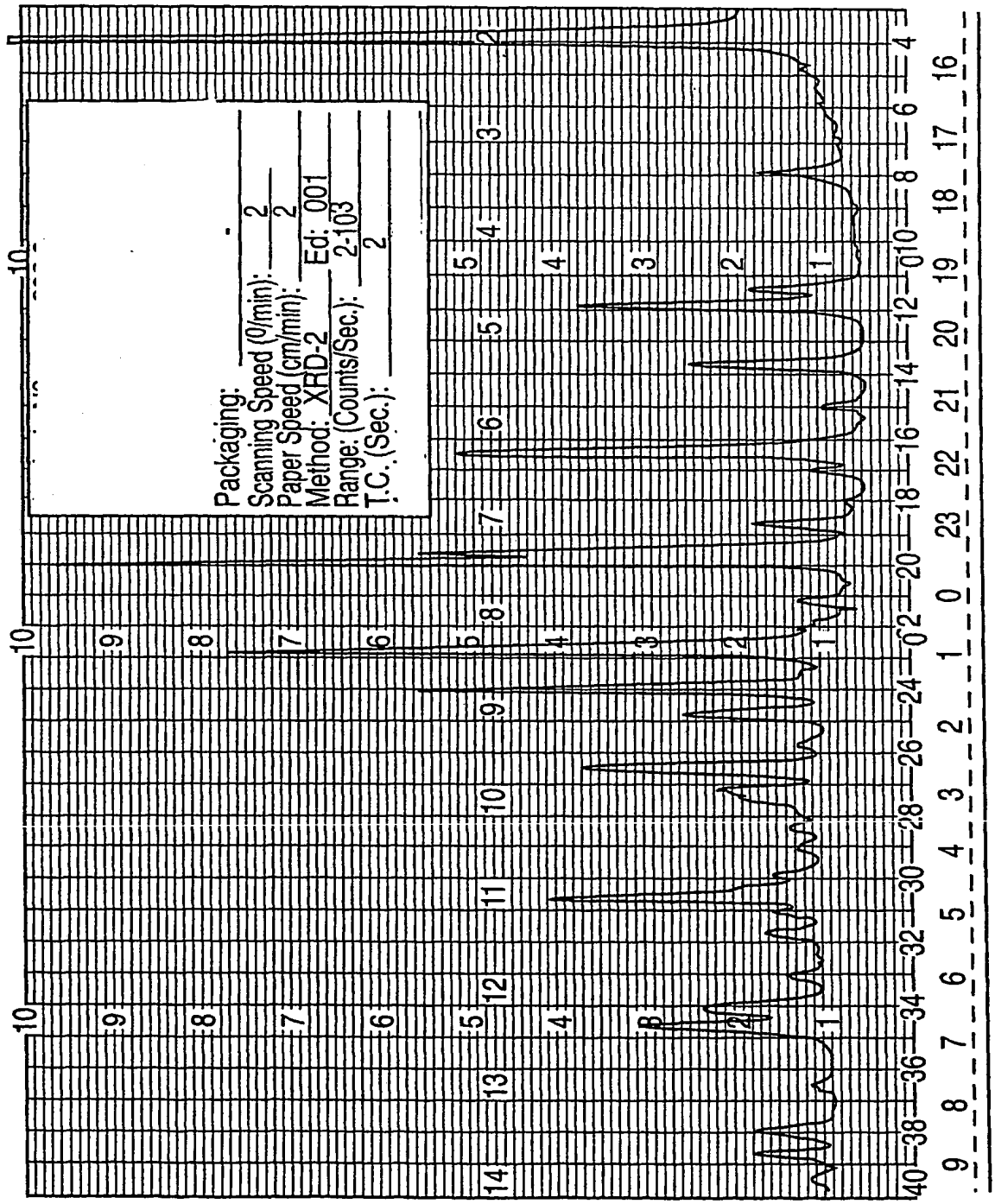


FIG. 8

XRD DATA
FOR FORM VI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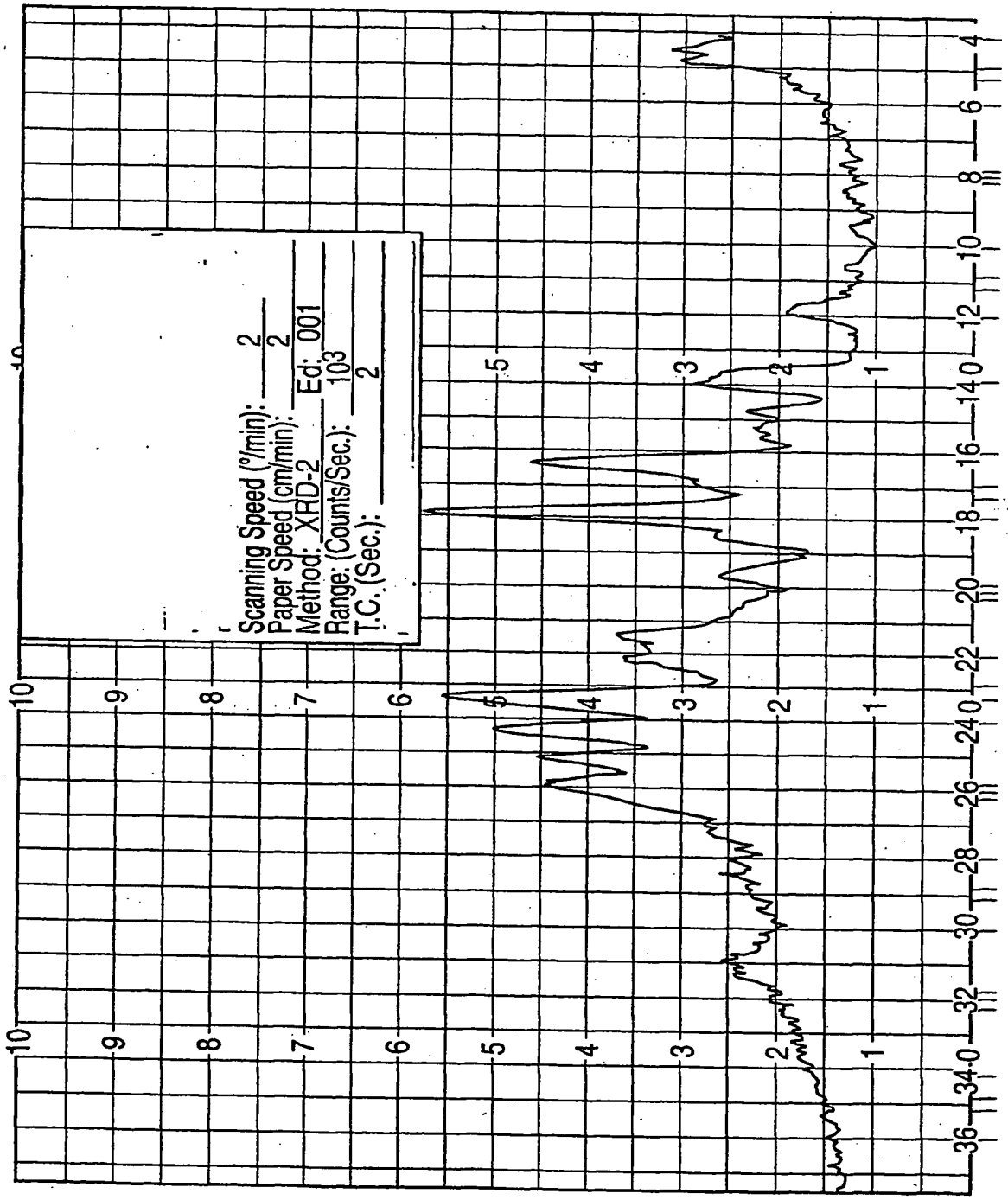
T.C. (Sec.): 2

FIG. 9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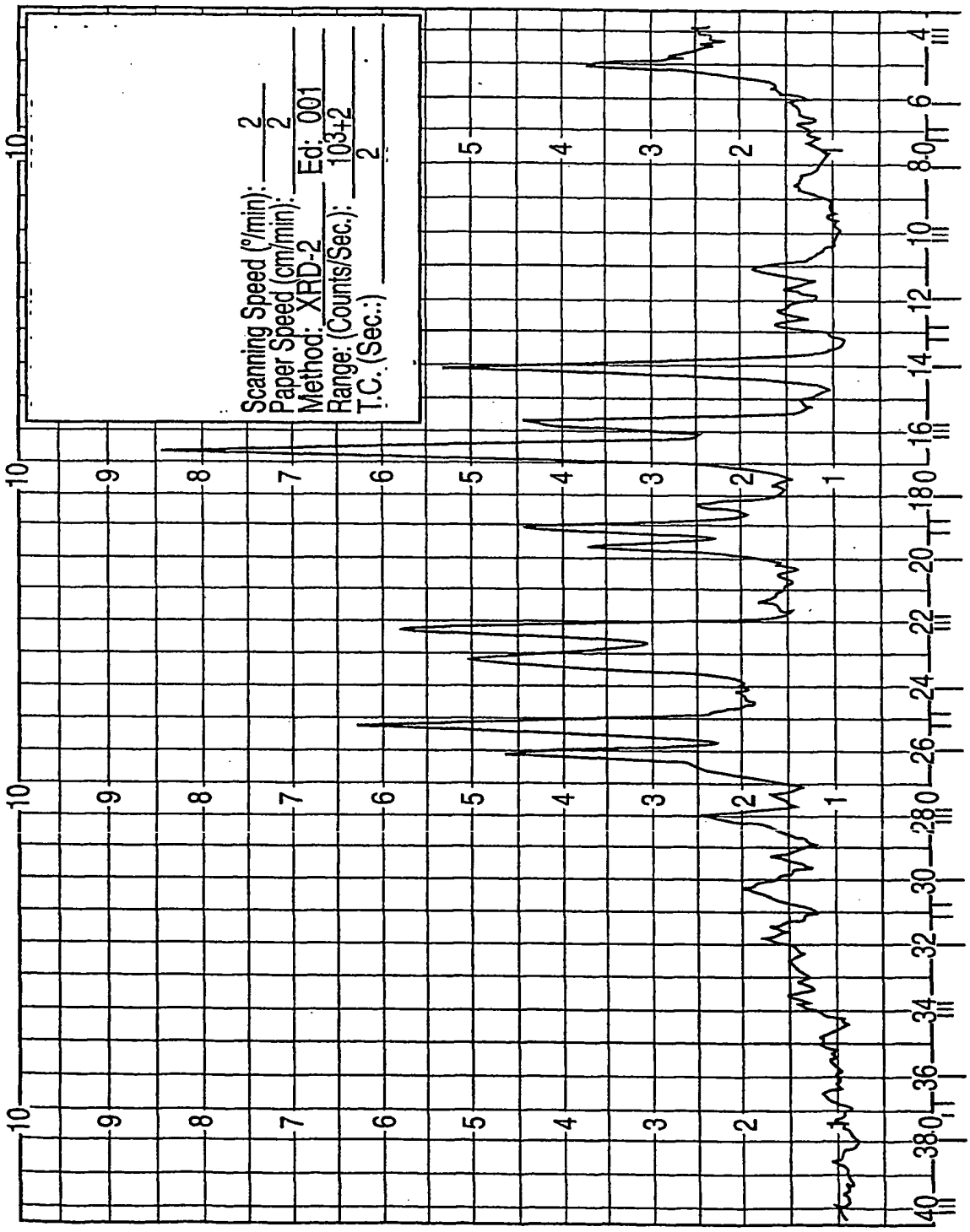
T.C. (Sec.): 2

FIG. 10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T.C. (Sec.:) 2

FIG. 11

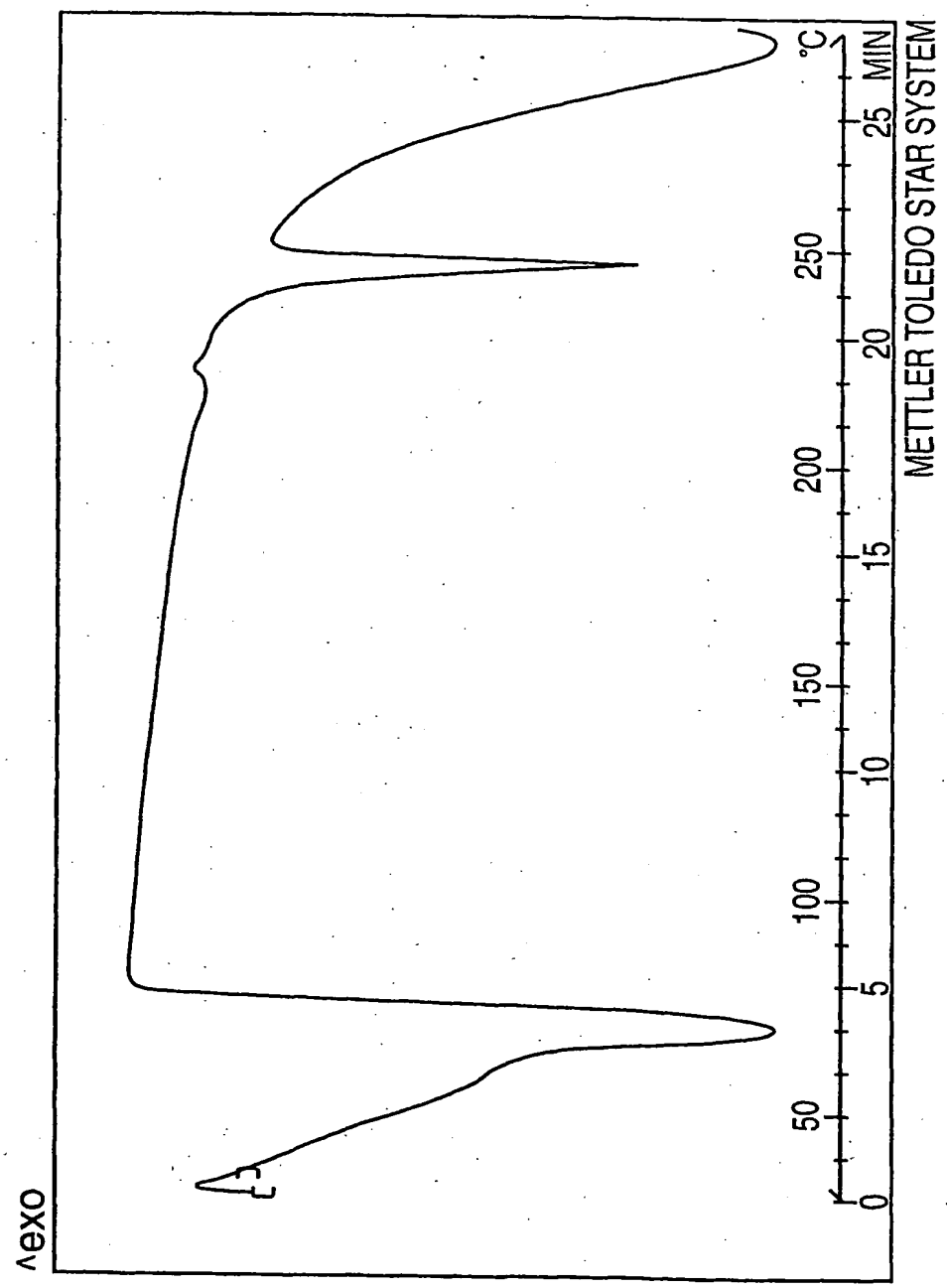

METTLER TOLEDO STAR SYSTEM
°C
MIN
0
50
100
150
200
250
5
10
15
20
25
exo

FIG. 12

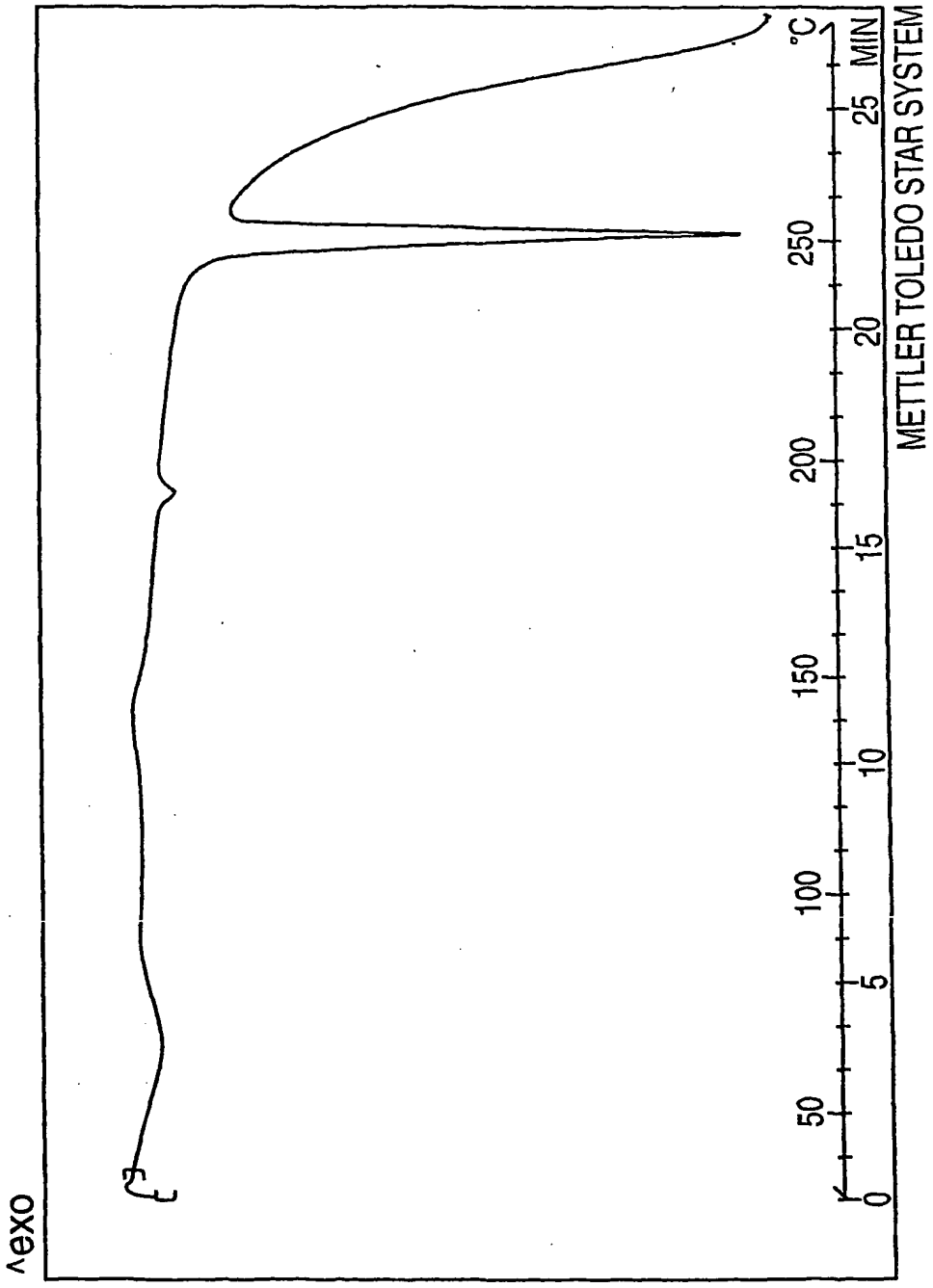
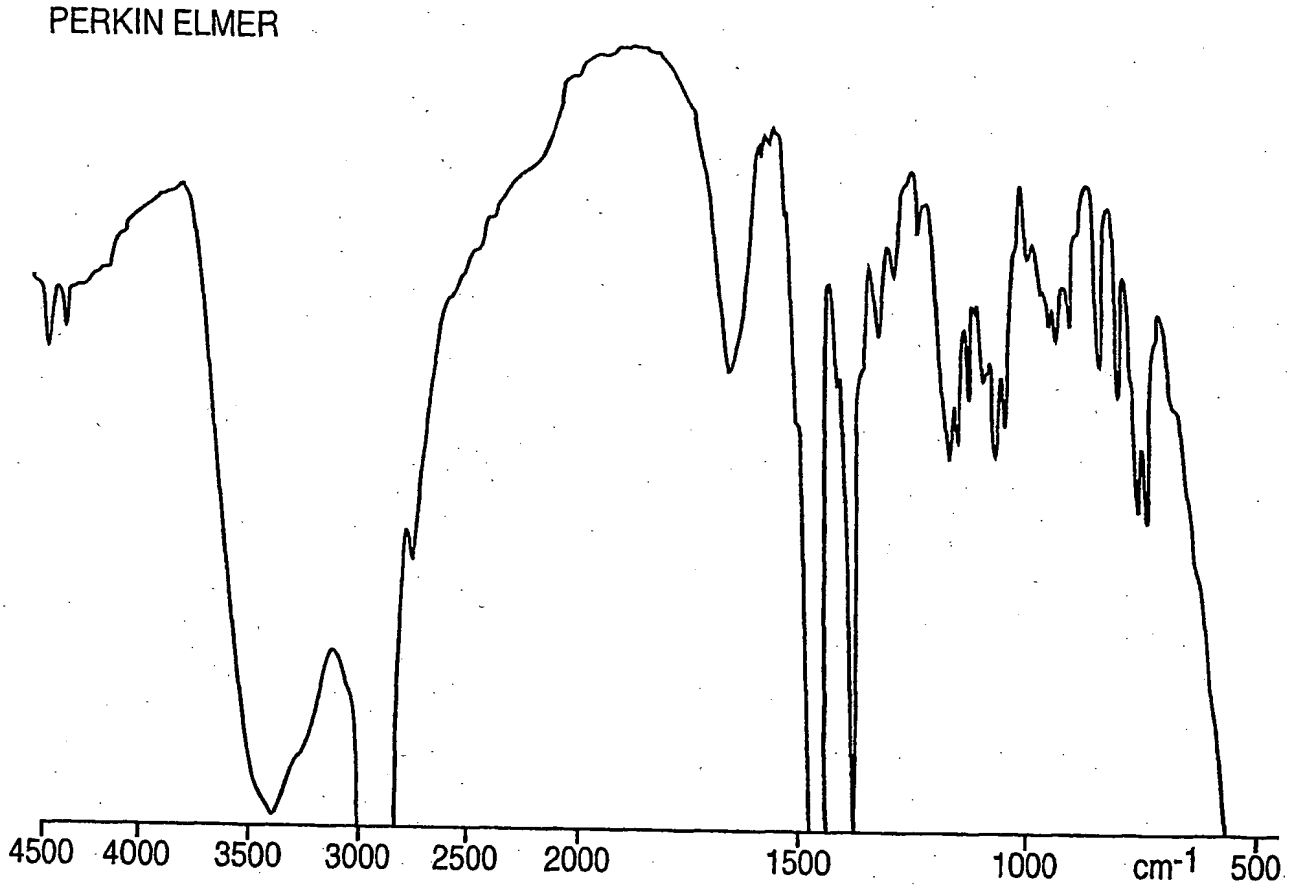
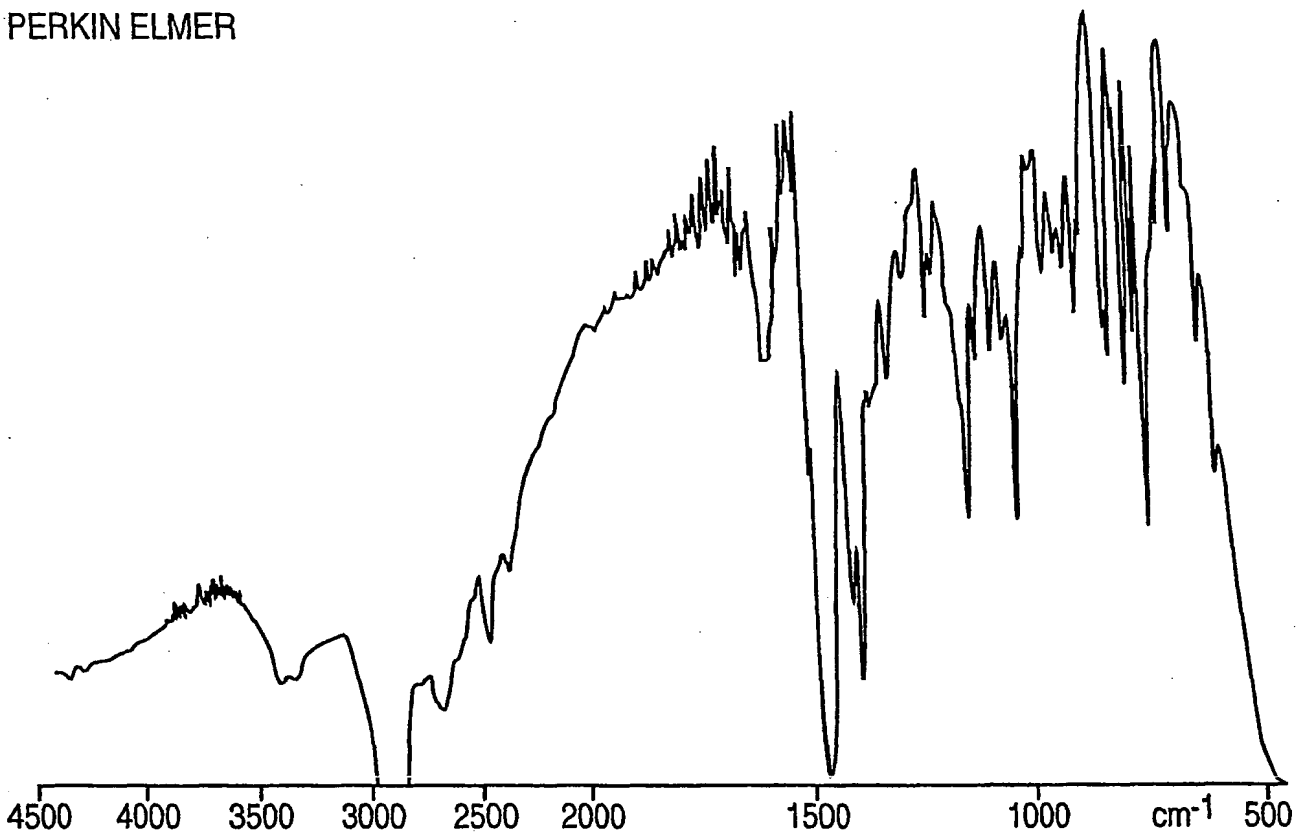

METTLER TOLEDO STAR SYSTEM
°C
MIN
50
100
150
200
250
0
5
10
15
20
25
^exo

FIG. 13



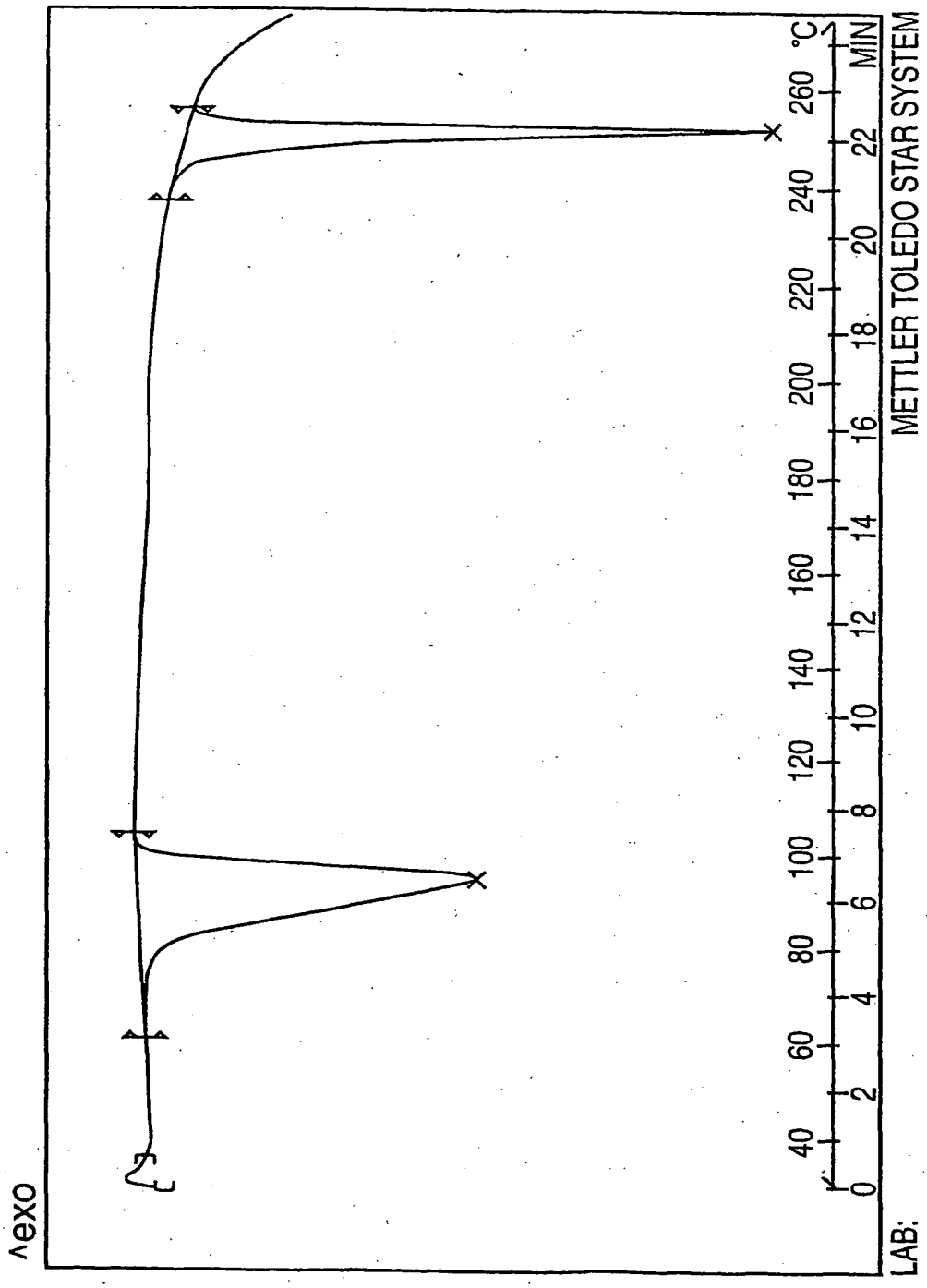
16 SCANS, 4.0cm-1
SRT HCL mm-686-1 NUJOL

FIG. 14



16 SCANS, 4.0cm-1
SRT HCL TN 1641-1 NUJOL

FIG. 15



DSC OF FORM VI ETHANOLATE

FIG. 16

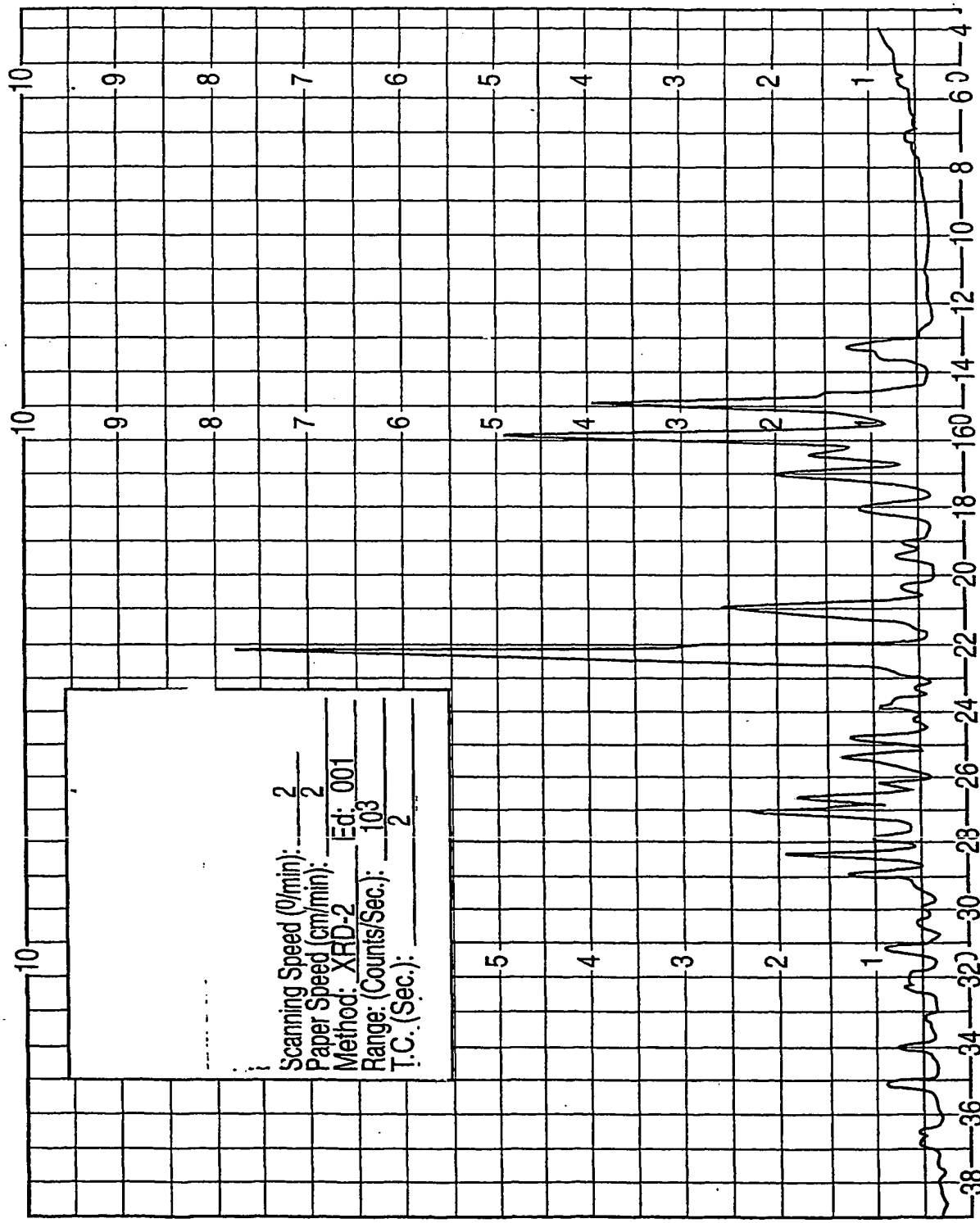
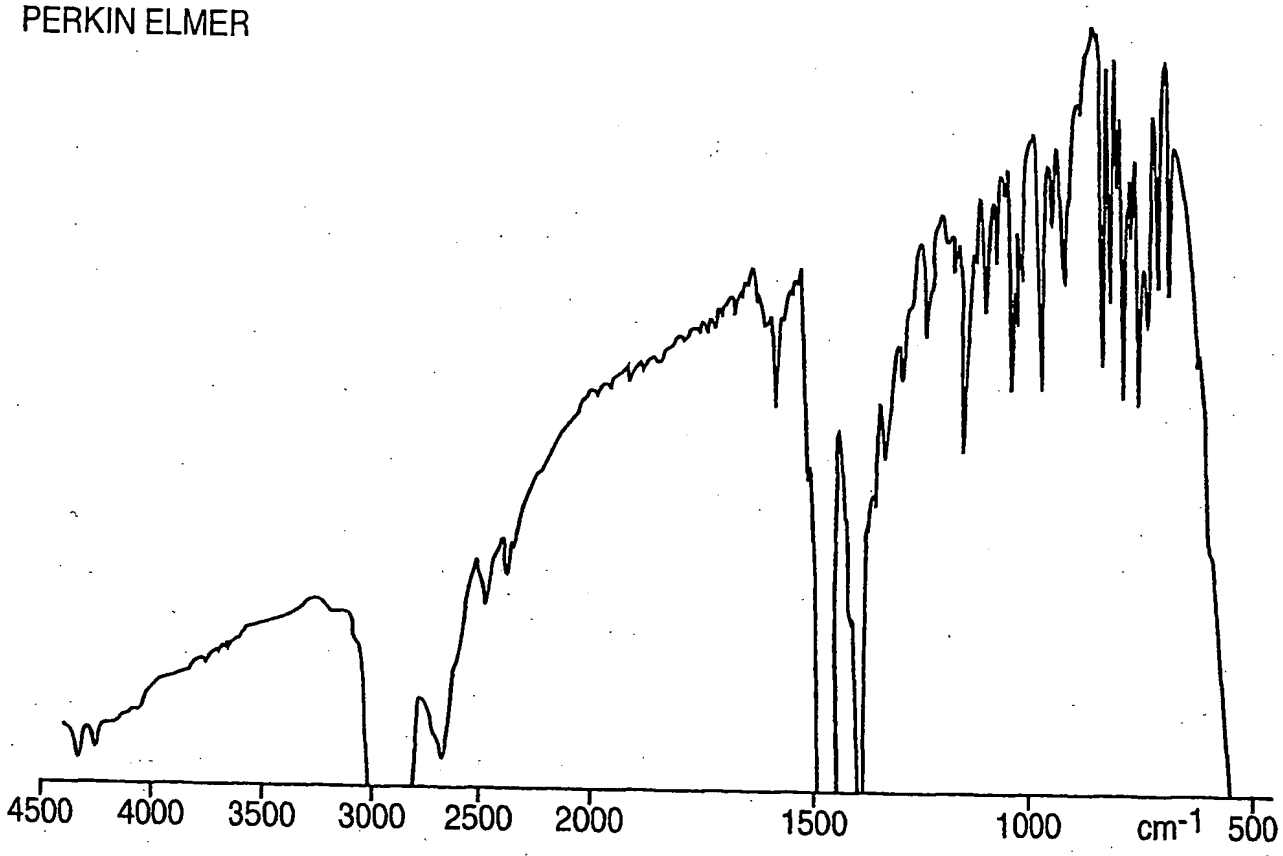
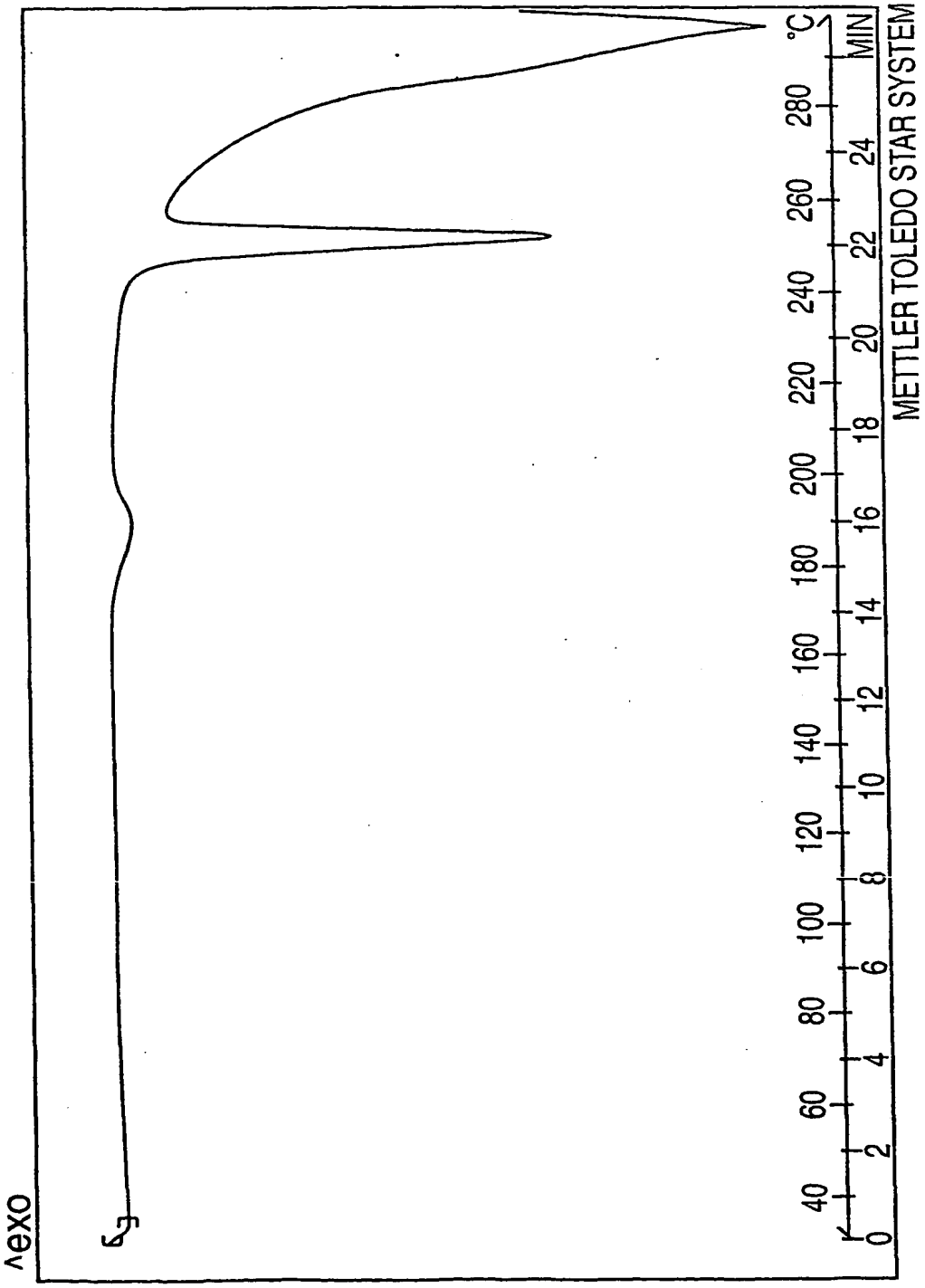

Scanning Speed (0/min): 2
Paper Speed (cm/min): 2
Method: XRD-2 Ed: 001
Range: (Counts/Sec.): 103
T.C.(Sec.): 2
X-RAY POWDER DIFFRACTOGRAM OF SERTRALINE HCL NOVEL FORM X FOR PATENT

FIG. 17



FTIR SPECTRUM OF SERTRALINE HCL FORM X FOR PATENT

FIG. 18



DSC OF FORM X

FIG. 19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/47546

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07C 211/42
US CL : 564/308

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 564/308

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,248,699 A (SYSKO et al) 28 September 1993 (20.09.1993).	1-54
A	US 4,536,518 A (WELCH, JR. et al) 20 August 1985 (20.08.1985).	1-54

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 March 2002 (05.03.2002)	12 APR 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Valerie Bell-Harris for Samuel A Barts Telephone No. 703-308-1235

Form PCT/ISA/210 (second sheet) (July 1998)